

Synthesis and characterisation of conductive PEDOT derivatives for biomedical applications

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Statement of Originality

I confirm the work stated herein was all conducted by myself both in the South Kensington campus of Imperial College London and the Tokyo Institute of Technology and is my own original research. Any contributions from others are referenced clearly in the text.

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Contributions

Chapter 2 – Thanks to Dr James Ponder for advice in synthesis and guidance in collecting cyclic voltammetry data. Some of the compounds used early on in this project were also made by Dr Christopher Spicer (although they were all re-synthesised by the author). Thanks goes to James Foote for help in synthesis of a number of the small molecules and polymers discussed.

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Abstract

Poly(3,4-ethylenedioxythiophene) (PEDOT) has established itself as the conducting polymer of choice for bioengineering applications in recent years owing to its excellent stability, biocompatibility, and exceptional conductivity. Though extraordinary, several drawbacks still limit its full potential in biological systems, including sub-optimal mechanical properties, bioactivity and degradation. In this thesis, PEDOT is taken back to the drawing board to design and synthesise innovative new derivatives and increase its utility in biomedicine still further.

In the first half of the thesis, conventional covalent polymer derivatives are explored. In Chapter 2 the problem of degradation is approached, and a range of design options presented and characterised. Chapter 3 outlines the synthetic derivations that have been pursued in adding functionality to PEDOT-based backbones. This should allow for its use in a number of new avenues of biomaterials such as organic electrochemical transistors and 3D printing.

The latter half addresses supramolecular systems. In Chapter 4 the monomeric form, 3,4-ethylenedioxythiophene (EDOT), is incorporated into a self-assembling hydrogel system with full characterisation and elucidation of structure-property relationships. Chapter 5 moves to look at a quite different self-assembling system. A related polymer poly(9,9-dioctylfluorene-*alt*-benzothiadiazole) (F8BT) decorated with poly(ethylene glycol) (PEG) chains is shown to assemble into unprecedented fractal structures. The dependence of such structures on assembly conditions and PEG chain length is explored and mechanisms proposed with the aid of simulations.

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Abbreviations

°	Degrees
15-crown-5	1,4,7,10,13-Pentaoxacyclopentadecane
16-crown-6	1,4,7,10,13,16-hexaoxacyclooctadecane
Å	Angstrom
AFM	Atomic force microscopy
Asp/D	Aspartic acid
BHJ	Bulk heterojunction
CD	Circular Dichroism
CHCl ₃	Chloroform
CV	Cyclic voltametry
D ₂ O	Deuterium oxide
DMSO-d ₆	Deuterated dimethylsulfoxide
DCM	Dichloromethane
DFT	Density functional theory
DHAP	Direct(hetero) arylation polymerisation
DI	Deionised
DLS	Dynamice light scattering
DMAc	<i>N,N</i> -Dimethylacetamide
DMF	<i>N,N</i> -Dimethylformamide
DMSO	Dimethylsulfoxide
E _g	Band gap
ESI	Electrospray ionisation
eV	Electron volts
EWG	Electron withdrawing group
F8BT	Poly(9,9-dioctylfluorene- <i>alt</i> -benzothiadiazole)
FT-IR	Fourier transform infrared
Gly/G	Glycine
GPC	Gel permeation chromatography
GS	Ground state
h	Hours
HOMO	Highest occupied molecular orbital
IP	Ionisation potential
kDa	Kilodalton
LUMO	Lowest unoccupied molecular orbital
m/z	Mass to charge ratio
MALDI-TOF	Matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry
MeOH	Methanol
MgSO ₄	Magnesium sulfate
min	Minutes
MQ	MilliQ water
M _w	Weight average molecular weight
NBS	<i>N</i> -Bromosuccinimide
NIR	Near-infrared
nm	Nanometer
NMR	Nuclear magnetic resonance

OPV	Organic photovoltaic
PANi	Polyaniline
PEDOT:PSS	Poly(3,4-ethylenedioxythiophene):Poly(styrene sulfonate)
PEG	Polyethylene glycol
Phe/F	Phenylalanine
PL	Photoluminescence
ppm	Parts per million
Ppy	Polypyrrole
ProDOT	3,4-propylenedioxythiophene
Rotavap	Rotary evaporator
SANS	Small angle neutron scattering
SAXS	Small angle X-ray scattering
SEM	Scanning electron microscopy
S _N Ar	Nucleophilic aromatic substitution
TEM	Transition electron microscopy
THF	Tetrahydrofuran
UV-vis	Ultraviolet/visible
δ	Chemical shift
ε	Extinction coefficient
μ	Micron

“The only thing better than finding something you’re looking for,
is finding something you weren’t looking for at a great bargain”

- Uncle Iroh, ATLA

Chapter 1 - Introduction

1.1 - The physics of semiconducting and conducting polymers

Since this thesis will explore extensively the charge transport of organic polymer systems, it is prudent to grasp the underpinning physical processes as such intuition will inform system design, processing and understanding. This section will therefore outline basic solid-state semiconductor/conductor physics and optoelectronic theory as well as proposed mechanisms of conduction in conjugated systems.

1.1.1 - Introduction to conjugated systems

To understand conducting polymer systems an understanding of the fundamentals in semiconducting polymer physics is required.

A useful model for insight into the observables of an electron in atoms or molecules is the orbital approximation. As dictated by the Pauli exclusion principle, every electron in a single quantum system (e.g. an ethene molecule) must occupy a unique state as defined by the 4 quantum numbers: the principal quantum number (n), angular momentum (l), magnetic moment (m_l) and spin (m_s). Various permutations of these will result in specific geometries of probability density known as orbitals. Overlap of adjacent orbitals will yield two possible types of result, an in-phase, low energy combination (bonding orbital) and a higher energy, out-of-phase combination (the antibonding orbital). For a covalently linked molecule in the ground state, orbitals will be filled from the lowest energy state up meaning most if not all will be bonding molecular orbitals. When considering the entire molecule, all the electron orbitals, whether participating in bonding or otherwise, can be thought of as a ladder of energies from the s_1 -orbitals at the lowest energy to the various bonding orbitals at higher energies. The filled state of highest energy is known as the highest occupied molecular orbital (HOMO) while the empty state just above the orbital of lowest energy is termed the lowest unoccupied molecular orbital (LUMO).

Taking a simple idealised molecule such as ethene (see **Figure 1-1a**) the sigma (σ) bonding and (σ^*) antibonding states sit both below and above the pi (π) bonding and (π^*) antibonding states respectively (**Figure 1-1c**). In contrast to the head-to-head overlap of σ -orbitals, π -orbitals result from the side-by-side, in-phase overlap of p_z orbitals with less bonding character and lower stability (**Figure 1-1b**). Therefore, as shown in **Figure 1-1c**, the π orbitals are the highest in energy to be occupied whilst the π^* antibonding orbitals are the lowest to not be occupied (least overlap in antibonding case creates lowest energy penalty). As such, these orbitals are the HOMO and LUMO of this system in the ground state. The π - π^* transition is therefore the lowest energy excitation that might be induced in this system and accordingly would correspond to the longest wavelength of irradiation the molecule would absorb.

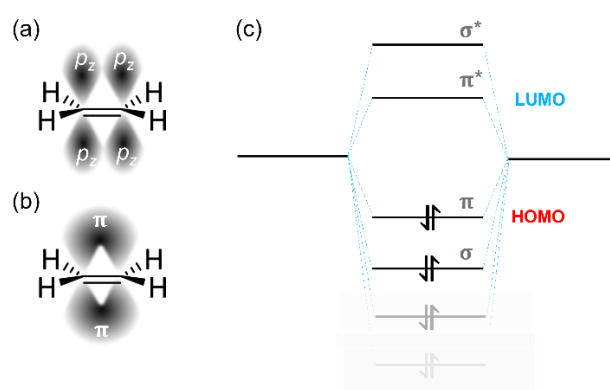


Figure 1-1. (a) Illustration of how p_z orbitals would look if hypothetically non-interacting/overlapping and (b) how they are predicted to be when overlapping to form pi (π) orbitals. (c) Representation of the molecular orbital diagram for ethene.

More generally, conjugated systems comprise alternating double and single bonds along the length of the polymer's sp^2 hybridised carbon backbone. Where an sp^3 hybridised chain displays only σ bonds, a sp^2 hybridised system exhibits additional π orbitals orthogonal to the local σ bonding network holding the backbone together. Depending on the orientation of these π orbitals, they will overlap to a greater or lesser degree allowing the electrons occupying them to share probability density with each other. In theory, a perfectly conjugated system would delocalise the electron density across the entire chain length. In practice, however, the conjugation is broken by structural artefacts such as twists in the backbone, limiting this delocalisation phenomena to just short oligomeric segments of the polymer chains.¹

Energetically, new sp^2 centres added to a delocalised system will be prevented from having identical energy states to those already present in the system by exclusion rules. They will therefore split into a progressively more densely populated collection of states pushing the HOMO and LUMO closer together. As the chain is extended indefinitely the states will become so numerous as to resemble a continuous *band of energies*, as shown in **Figure 1-2**. Rather than thinking in terms of HOMO and LUMO, though they still exist at the band edges, it often becomes more useful in semiconductor physics to refer to them as the valance band and conduction band of the molecule. The former at 0 K would have the HOMO as its highest state while the latter the LUMO as its lowest.

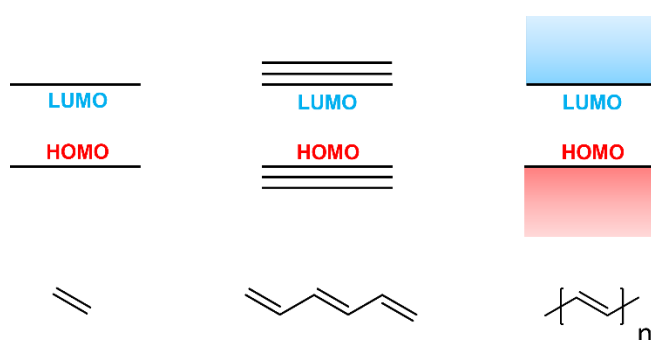


Figure 1-2. Diagram illustrating the increasing density of states as the number of π interactions participating in the conjugation is increased from 1, to 3, to infinity.

In solid state physics the energy of the HOMO at absolute zero is also referred to as the Fermi energy. When considering systems at $T > 0$ K however, the sharp distinction between occupied and unoccupied states is blurred requiring a new quantity, the *Fermi level*, to be defined. This is defined as the energy at which a state has a 50% chance of being occupied. The distribution of occupancy in the material can be expressed by the Fermi-Dirac distribution to give the population, P , of the orbitals:

$$P = \frac{1}{e^{(E-\mu)/kT} + 1} \quad (\text{Eq. 1-1})$$

Where E is the energy, μ is the chemical potential, k the Boltzmann constant and T is temperature. Unlike the fermi energy, the fermi level is a function of temperature and is the energy at which $P = 0.5$.

1.1.2 - The infinite chain and origin of the band gap

Based on the conjugated system described thus far it would be expected that extending a conjugated system narrows the gap (albeit non-linearly) between the HOMO and LUMO. Considering a conjugated system of an infinite chain length, it would be anticipated that such a gap would vanish. The resulting system would comprise of a continuous set of energy states that *contains* the fermi level i.e. a 1-dimensional metal. In practice, inspection of the quantum mechanics indicates that this cannot be so even in theory. To understand this a 1-dimensional metal will first be examined.

If we consider an electron in a system of approximately constant potential, $U(x)$, it can be shown that the allowed energy states can be described by the free electron model giving an energy-wavevector (ϵ - k) relation shown in **Figure 1-3**.

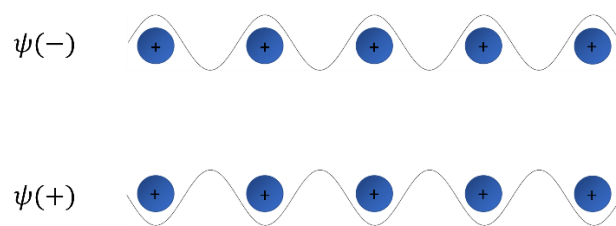


Figure 1-3. Depiction of the two possible wavefunctions at a wavelength of the periodic potential.

The introduction of periodic inhomogeneities in the potential requires the consideration of Bragg reflection contributions (the phenomena by which changes in potential reflect wavefunctions with a certain probability).² Here, to allow for the series of reflections travelling in opposite directions and assuming such travelling waves might be described by $e^{i\pi x/a}$ and $e^{-i\pi x/a}$, the solutions must be standing waves of the form:

$$\psi(+) = e^{i\pi x/a} + e^{-i\pi x/a} = 2\cos(\pi x/a) \quad (\text{Eq. 1-2})$$

$$\psi(-) = e^{i\pi x/a} - e^{-i\pi x/a} = 2i\sin(\pi x/a) \quad (\text{Eq. 1-3})$$

Where a is the lattice spacing. Physically this corresponds to electron density localising either *on* the positive potential changes or *between* them (**Figure 1-3**). Clearly the intuition from coulombic

attraction would say having electron density kept between the positive potential changes will require more energy than coalescing around them. By noting the frequencies of these states are identical yet their energies are not, it can be inferred states with energies between the two are forbidden. This non-negligible difference in energy is the band gap of the system.²

To apply this to semiconducting polymers, in the same way that a periodic potential can arise in the regularly arranged positive ions in a 'sea' of electrons of a crystalline metal, so the *periodic distortion* from alternating bond lengths in a theoretical, predominantly neutral, infinite conjugated polymer such as polyacetylene will create a region of forbidden energy states: i.e. the band gap. This is known as the *Peierls distortion*.

Attempts to model the charge transport in semiconducting/conducting polymers have been met with various complications however, broadly speaking the following is true. In metals, the presence of the fermi level within a set of continuous states requires negligible energy to transition so charge transport is possible even at very low temperatures. However, increasing the temperature increases the vibration (i.e. transitions to higher vibronic states) of the positive atomic metal, impeding the movement of electrons and as such metals are expected to decrease their conductivity with temperature (up to the Mott-Ioffe-Regel limit).¹ Conversely, semiconductors rely primarily on the thermally activated promotion of charge carriers into the conduction band and thus their conductivity is expected to increase with temperature.

1.1.3 - From semiconducting to conducting polymers

The field of conducting polymers started with work in the late 70s when Heeger, MacDiarmid and Shairakawa first recorded the remarkable increase in conductivity of polyacetylene as a result of halogen doping.³ This seminal work led to the class of doped conjugated organic polymers that followed to be termed 'synthetic metals'.

To understand the doping phenomena the concept of conductivity must first be examined. While classically we might think of the electron like a billiard ball jostling around the material, free to respond to an applied potential, quantum mechanics predicts that the particle's bound nature means it must be found localised to a particular volume, the $|\psi|^2$ as illustrated by orbitals. To move throughout the material, the charge carrier must therefore transition through a multitude of different, discrete bound states and as such these orbitals must be both empty and within the energetic 'reach' of the particle.

It is clear then that electrons in metals or the conduction band of semiconductors that are surrounded by many free states of negligible difference in energy can move 'freely'.

Doping in organic semiconductors refers to the oxidation (or reduction) of the polymer backbone introducing positive (or negative) charges and creating a p-type (or n-type) conductive material. In the more common p-type case, at low doping concentrations, removing an electron will proceed as a Franck-Condon like ionisation mechanism (where the nuclei are assumed to be stationary relative to the electrons) following which the polymer will relax into its equilibrium geometry in the charged state. Whether the charge remains coupled to a localised distortion in the polymer, known as a *polaron*, will depend on the energy saved by the narrowing of the HOMO-LUMO gap in the excited state relative to the ground state, $\Delta\varepsilon$. If this energy saving is greater than that required to *make the distortion* (E_{dis}), then a polaron is formed. The polaron binding energy relates to the difference in these quantities:

$$|\Delta\varepsilon| - |E_{dis}| = E_{pol} \quad (\text{Eq. 1-4})$$

If and only if E_{pol} is > 0 , otherwise there is no polaron formation. At low doping concentrations, this phenomenon is strictly localised and as such should be considered as energy states within the band gap rather than a narrowing of the band gap. Similarly, the removal of a second electron from the same segment such that the positive charge left is associated with the same structural distortion is termed a *bipolaron* and is often more energetically favourable than two separate polarons. The resulting states reside even deeper in the band gap and so might be detected as absorption at even longer wavelengths. Upon increasing the doping concentration, it has generally been observed that bipolarons begin to dominate over polarons and the localised bipolaron states begin to merge and form extended bands.⁴⁻⁶ Since the lower of these is populated with charge carriers the material behaves as if it has a significantly reduced band gap, i.e. the difference in the bipolaron bands, and hence exhibits much higher conductivities. In the case of polythiophenes and derivatives, metallic behaviour has even been observed corresponding to the actual merging of the upper and lower bipolaronic bands and complete erasure of the band gap.⁷

1.1.4 - Barriers to conduction and charge transport mechanisms

The transport of charge through conjugated polymer materials is met by a range of barriers that can significantly reduce conductivity. Some are avoidable by a detailed understanding of the microstructure and processing conditions that lead to it, whilst others will always be present to some extent. Disorder within the polymer chains from backbone bending/twisting and subsequent conjugation breaking can not only impede mobility along the chain but also potentially act as trapped states. Trapped states are those significantly lower in energy than the fermi energy of a material into which charges can fall but, given the high occupancy of states surrounding it, will struggle to get out of. This reduction in charge carrier density hinders the performance of many types of devices and is a constant consideration when designing and processing semiconducting/conducting systems. Approaches at the micron scale, such as annealing to reduce disorder, and the molecular scale, e.g. incorporation of bridging groups to reduce twisting and promote planarity, can be used to combat these deleterious artefacts.

A good example of an unavoidable factor is the *inter*-chain transport whereupon the electrons/holes have to 'jump' from one polymer chain to another. Even in the best thin films this factor will still have to be contended with and will likely be rate limiting. Arguably a more controllable area is the charge transport between conjugated polymer domains in the microstructure, an area that can be governed to some extent by the processing conditions used.¹

1.1.5 - Models of transport

Several models have been proposed to relate conjugated polymer nano and microstructure to the transport mechanisms. Initially, as shown in **Figure 1-4a**, Mott's variable range hopping (VRH) model was used that described the charges as hopping between chains to vacant sites as a function of distance and energy difference (**Eq. 1-5**).⁸

$$\sigma_{VRH}(T) = \sigma_0 \exp \left[- \left(\frac{T_0}{T} \right)^{\frac{1}{n+1}} \right] \quad (\text{Eq. 1-5})$$

Where T_0 is a temperature related to the activation energy, σ_0 represents the overall conductivity. Whilst describing disordered semiconductors adequately this model did not fit the near-metallic data from poly(acetylene), poly(aniline) and poly(3,4-ethylenedioxythiophene) at high doping concentrations.⁹⁻¹³

To address this Sheng et al. developed the fluctuation-induced tunnelling model that described the systems as behaving like large, conductive grains situated in a dielectric-like medium that exchange charge through tunnelling (**Eq. 1-6**).^{14,15} The tunnelling described here is not the quantum mechanical phenomena but rather describes a thermally activated transfer of a charge from one 'metallic' grain to another (**Figure 1-4b**).

$$\sigma_{sheng}(T) = \sigma_s \exp\left(-\frac{T_1}{T + T_2}\right) \quad (\text{Eq. 1-6})$$

Where σ_s , T_1 and T_2 are constants, the latter two of which relate to the geometry and energy of the barrier.¹

A crucial difference in these models is that where the former assumes strictly localised polaronic states that 'hop' between each other, the latter describes clusters of polaronic states that behave, within the cluster, in a delocalised pseudo-metallic fashion, behaviour that seems closer to reality in highly doped systems.

Recently a model has been put forward by Kang and Snyder that unites the concepts presented above by using Fermi-Dirac statistics to define energy states that contribute to the conduction. By combining conductivity estimations through electronic and thermoelectric methods, meaningful approximations of the material energy states could be compared to the model.¹⁶

Such a summary of the modelling approaches used in the field is far from exhaustive but it is hoped outlining the most prominent will give some sense as to the factors to consider in designing conductive systems. Now some understanding of charge transport in organic conjugated systems has been gained, an appreciation of their utility in a biological setting can be explored.

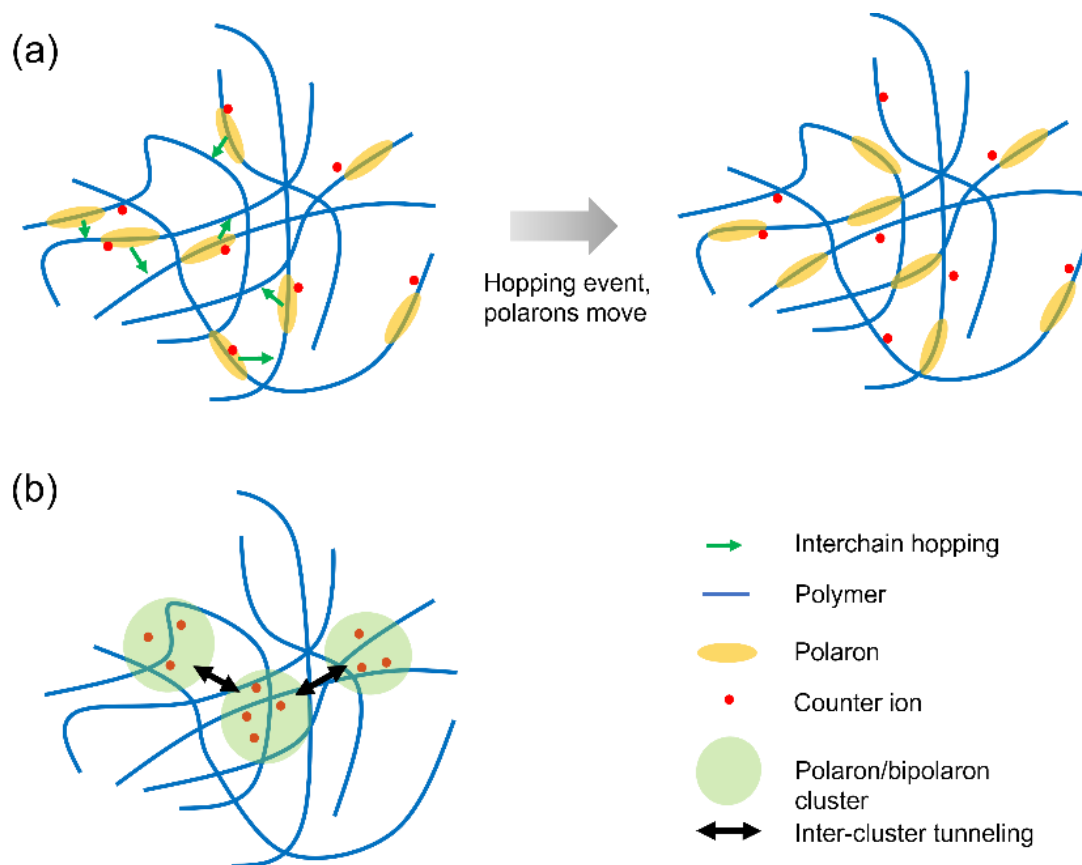


Figure 1-4. Figure illustrating (a) the variable hopping model (VHM) whereby polarons migrate between chains by hopping events and (b) the polaron 'tunnelling' model whereby polarons/bipolarons exist as clusters and if close enough are able to tunnel between one another facilitating charge transport. Figure redrawn from Gueye et al.¹

1.2 - Conductive polymers (CPs) in biomaterials

Conductive materials are of great interest to the biomedical field in areas including tissue scaffolds, where electrical stimulation can improve differentiation and proliferation of appropriate cell types (cardiac, neural etc.), electrode interfaces, to improve bio-integration, and biosensors to name a few. For some years now conductive organic polymeric systems have been of great interest to those working in biomaterial disciplines concerned with electroactive biological systems.¹⁷ Their utility comes through the ability of such materials to be readily synthesised, functionalised, modified and processed as well as presenting the possibility of property control through stimulation.^{18–21} Already the community has utilised a substantial list of different CP systems (see **Table 1-1**) with a variety of dopants including both small molecules and bio-molecules. Within this set, several CPs have established themselves as prominent in the bioengineering field and will be addressed individually below.

Table 1-1. A non-exhaustive list of polymers investigated for biomaterial and tissue engineering applications. Rewritten from Balint et al.¹⁷

Polymer name	Abbreviation
Polypyrrole	PPy
Polyaniline	PANi
Poly(3,4-ethylenedioxythiophene)	PEDOT
Polythiophene	PTh
Polythiophene-vinylene	PTh-V
Poly(p-phenylene)	PPP
Poly(3-alkylthiophene)	PAT
Poly(2,5-thienylenevinylene)	PTV
Poly-p-phenylene-sulphide	PPS
Polyacetylene	PAC
Polyfuran	PFu

1.2.1 - Polypyrrole

Polypyrrole (PPy), shown in **Figure 1-5**, is possibly the most commonly studied CP system today. Its advantages include an ease of synthesis in a range of solvent systems²²⁻²⁴, excellent stability in ambient conditions^{25,26}, suitable conductivity^{22,24} and both *in vitro* and *in vivo* biocompatibility^{22,27,28}. More specifically, PPy has demonstrated good biocompatibility with a range of cell types including: Human endothelial cells,¹⁹ epidermal,²⁹ cardiac,^{17,30} Schwann,³¹ skeletal muscle³² and mesenchymal stem cells³³. PPy has therefore found use in biosensors^{20,34}, neural tissue engineering scaffold materials³⁵, nerve guide channels^{36,37}, blood conduits³⁸, neural probes³⁶ as well as delivery systems for drugs^{34,39}.

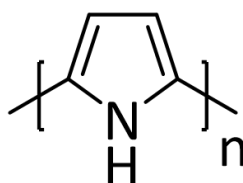


Figure 1-5. Schematic showing the structure of PPy

Within this large body of work can be found a plethora of methods to incorporate bio-functional molecules into CPs including physical entrapment in the polymer matrix¹⁹, absorption to the surface⁴⁰, covalent attachment⁴¹⁻⁴⁴ and even use as the dopant itself⁴⁵ as well as bio and non-bio molecular blends.^{17,30}

A particularly ingenious utilisation of PPy and demonstration of its potential can be seen from Gelmi et al.³² Here the authors utilised a dodecylbenzenesulfonate (DBS)-doped PPy system to demonstrate an architecture that showed the ability to not only transmit a periodic potential but also to swell and contract to that same pattern. Such a volume change was explained by the diffusion of ions into and out of PPy in response to changes in polymer doping/de-doping charge supplied by the fluctuating potential (**Figure 1-6**). Identification of various 'stemness' markers suggested such a dual action encouraged differentiation in induced pluripotent stem cells (iPSs).

Whilst promising and already seemingly ubiquitous, PPy suffers from inferior thermal stability and conductivity to its polythiophene-based, heterocyclic derivative counterparts possibly owing to an absence of electron withdrawing substituents that can deepen the energetic landscape and stabilise positive polaronic charge carriers.^{1,46}

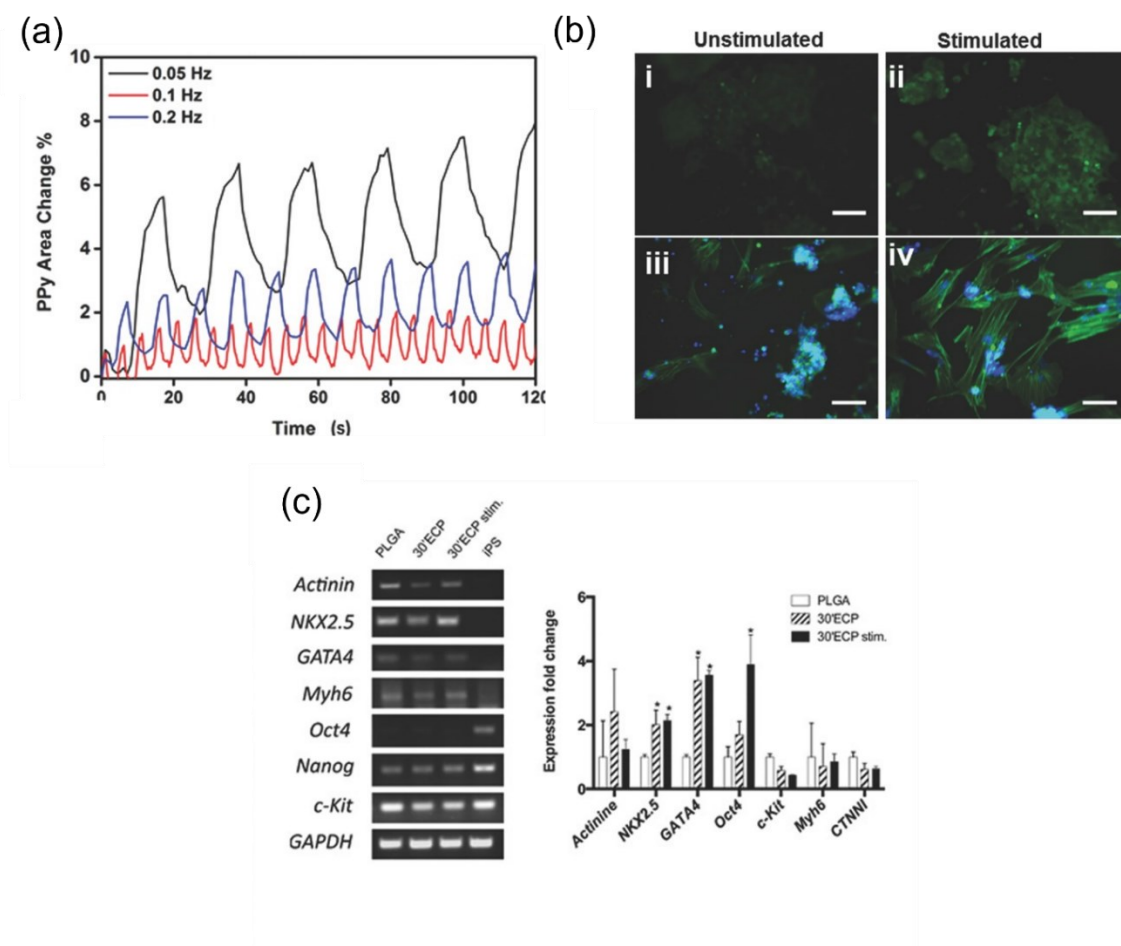


Figure 1-6. (a) The cyclic stimulation of the Ppy-based scaffolds was shown to elicit a corresponding actuation response at the same frequency. Here a biphasic potential waveform was applied by the authors at 0.05 Hz, 0.1 Hz and 0.2 Hz on electrochemically polymerised PPy-dodecylbenzenesulfonate nanofibers in PBS; (b) Comparison of cells seeded on the structures stimulated and unstimulated with (i/ii) live/dead staining and (iii/iv) actin filament staining. It was seen that induced pluripotent stem (iPS) cells subjected to periodic electrical and mechanical stimulation had a morphology more typical of smooth muscle cells; (c) This was further corroborated by an increase in cardiomyocyte markers Actinin, NKX2.5, Myh6 and GATA4 and decrease in stemness markers Oct4 and Nanog. Figure adapted and used with permission from Gelmi et al.³²

1.2.2 - Polyaniline

Polyaniline (PANI) has also received considerable attention in recent years.^{17,47} Interestingly, this polymer can exist in one of three redox states: the neutral, leucoemeraldine base; the half oxidised emeraldine base; and the fully oxidised pernigraniline base (**Figure 1-7**). It is most common to use this polymer in its emeraldine state since it provides the greatest stability and charge transport.^{34,48}

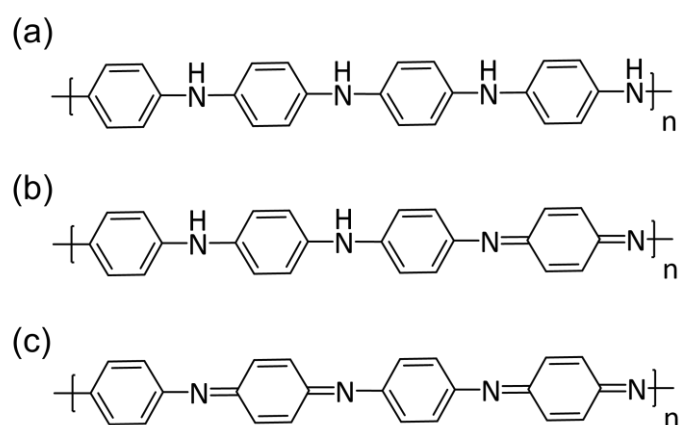


Figure 1-7. Schematic of the structure of PANi as: (a) its neutral, leucoemeraldine base; (b) its half-oxidised emeraldine base and; (c) its fully oxidised pernigraniline base.

Whilst PANi has been investigated for applications in neural probes, biosensors and tissue engineering its potential is limited by the chronic inflammation it can cause once placed in the body.⁴⁹ Indeed the use of PANi also requires the researcher to contend with a severely limited flexibility, processibility and lack of biodegradation.¹⁷

As with PPy, PANi has been combined with a host of different biomaterials including collagen⁵⁰, chitosan⁵¹, gelatin⁵² and synthetic materials, e.g. polyethylene glycol (PEG)⁵³ and block copolymer derivatives⁵⁴, to create conductive hybrid materials with improved bio-functionality and mechanical properties. Combination with biopolymers such as gelatin allows the material to be electrospun and for relevant morphologies such as fibres to be created.⁵² This is, however, inevitably to the detriment of the charge transport properties. Disadvantages include difficulty in functionalisation, potential toxicity of side products (particularly the dimer benzidine) and inferior conductivity when compared to polythiophene, derivatives as will be discussed.⁵⁵

1.3 - Poly(3,4-ethylenedioxythiophene): Poly(Styrene Sulfonate) (PEDOT:PSS)

1.3.1 - Discovery of PEDOT:PSS

After the ground-breaking work demonstrating *pseudo*-metallic properties of polyacetylene, efforts were directed toward improving the poor stability found in this and similar systems. Primarily these strategies centred around hetero-substitutions with electron withdrawing atoms/groups about the periphery of electron-rich aryl backbones, such as polythiophene, in order to deepen the oxidation potential just enough to provide ambient stability. The pioneering work done in the German Bayer Central Research Department appending di-oxy bridges to thiophene units eventually led to the first synthesis of poly(3,4-ethylenedioxythiophene) (PEDOT), a polymer that immediately proved itself both air-stable in the oxidised form and highly conductive (initial values measured at 200 S/cm^{-1}).^{56,57} Though promising, PEDOT alone was highly insoluble and difficult to process into devices. It was not until a fortuitous collaboration developing an antistatic coating in the presence of persulfates that the winning combination of PEDOT doped with poly(styrene sulfonate) (PSS) was finally found providing the workable, water soluble dispersion so commonly employed today (

Figure 1-8).⁵⁸

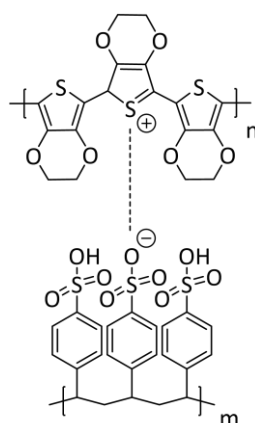


Figure 1-8. The structure of PEDOT:PSS

1.3.2 - Synthesis of PEDOT

Since its discovery, several synthetic avenues to PEDOT have been identified, the main categories of which can be summarised as below:

1. Transition metal catalysed polymerisation of di-halogenated EDOT monomers^{1,59}
2. Electrochemical polymerisation – uses a monomer, oxidant (in salt form) and often a layer of ITO, Au, carbon paper etc. as a surface for the polymerisation.^{60–63}
3. Direct (hetero)arylation polymerisation (DHAP)^{64,65}
4. Oxidative polymerisation^{1,66}

Electrochemical methods are particularly well suited for making thin films and rely upon a voltage bias along with an oxidant to oxidise the monomers, facilitating polymer growth on a substrate surface.¹ This technique will not be discussed in detail however, as solution-based polymerisation methods were deemed more appropriate for the work in this thesis via the considerable synthetic options available to create the required functional derivatives.

The latter of these four is arguably the most ubiquitous and manifests in the literature through a number of techniques. In solution, a number of catalysts have been explored primarily based on iron(III) complexes. The most commonly used of these is Fe(III) *para*-toluenesulfonate (Fe(Tos)₃). Although still under debate, the mechanism is believed to proceed in 3 stages (**Figure 1-9**): (i) Oxidation of EDOT monomer (Fe(III) to Fe(II)); (ii) combination of two oxidised monomers form a dimer that is subsequently deprotonated by water to complete conjugation; (iii) the process is repeated between dimers/oligomers to form the polymer.^{1, 67}

It was quickly found, however, that synthesis of just PEDOT resulted in a black, insoluble material that could not easily be processed.^{57,68} To combat this, researchers at Bayer AG polymerised PEDOT in a PSS electrolyte solution with persulfate as the oxidant.⁶⁹ The resulting dispersion PSS⁻ stabilised PEDOT⁺ could be processed more readily and show conductivities up to $4.8 \times 10^3 \text{ Scm}^{-1}$.

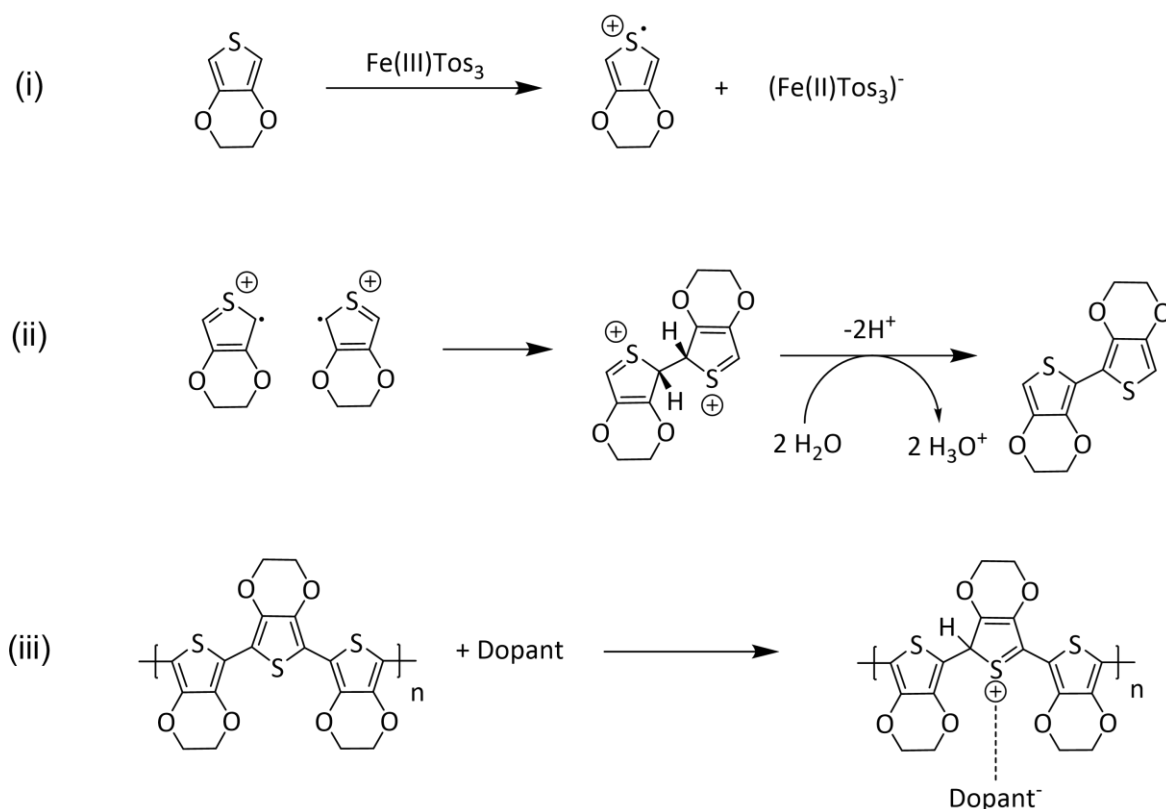


Figure 1-9. Schematic illustrating the proposed mechanism of oxidative polymerisation through (i) initial oxidation of an EDOT monomer; (ii) subsequent combination of oxidised monomers to give dimer formation following aqueous deprotonation; (iii) the final polymer is doped by oxidation and stabilised by the oxidant counter ion. Figure redrawn from Mueller et al.⁶⁷

In recent years, direct arylation chemistry has been increasingly employed to form conjugated polymer systems. The advantage of this over conventional cross-coupling chemistry stem from the stability of the Pd (II) catalyst, ease of monomer preparation and lack of the toxicity found in pendant metal centres of, for instance, Stille couplings. Direct arylation polymerisations (DARPs) can be applied to single component systems either through conventional conditions or with the aid of an oxidant (Oxi-DARP).⁷⁰ The advantage of the latter is the lack of a need for halogenation in the monomer precursor. For homo-polymerisations (both oxidative and directly arylated) only a single monomer constituent is used, limiting the amount of functionality and property tailoring that might be achieved. Use of more than one monomer type in such reactions would further result in a statistical mix and lack any precision in regiochemistry and polymer ordering.

An emerging alternative to this comes from direct (hetero)arylation polymerisation (DHAP). Here halogenated and non-halogenated comonomers are employed allowing for precise control of the subsequent ordering in the final polymer (E.g. ABAB structures). Halogenation of EDOT derivatives is tricky with the material being remarkably unstable and prone to oligomerisation. Adding just one more carbon into the dioxy- ring, however, drastically increases the handleability and as such

copolymerisation with mono/di-EDOTs and halogenated 3,4-propylenedioxythiophene (ProDOT) derivatives has allowed for a range of ordered, high molecular weight (M_w) and functional PEDOT derivatives to be easily synthesised (**Figure 1-10**).

Direct (hetero)arylation polymerisation

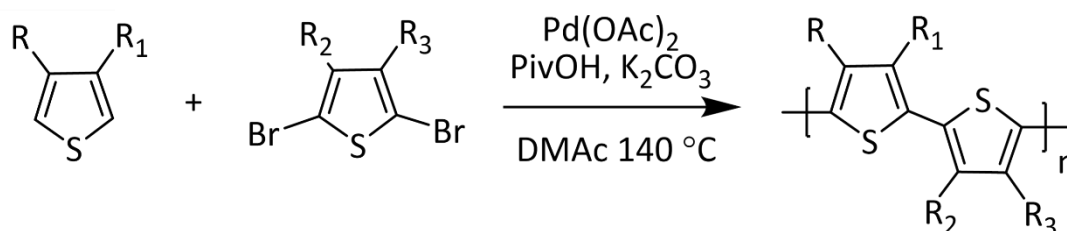


Figure 1-10. Synthetic scheme for direct(hetero) arylation polymerisation using thiophene derivatives. R groups would commonly be dioxy- bridges.

As depicted in **Figure 1-11**, the mechanism is thought to proceed through an oxidative addition/reductive elimination catalytic cycle similar to cross coupling chemistry.⁷¹ Crucially, the presence of a slightly sterically hindered carboxylic acid is believed to act as a proton shuttle, deprotonating the non-halogenated species (Ar') to allow its full coordination to the palladium.

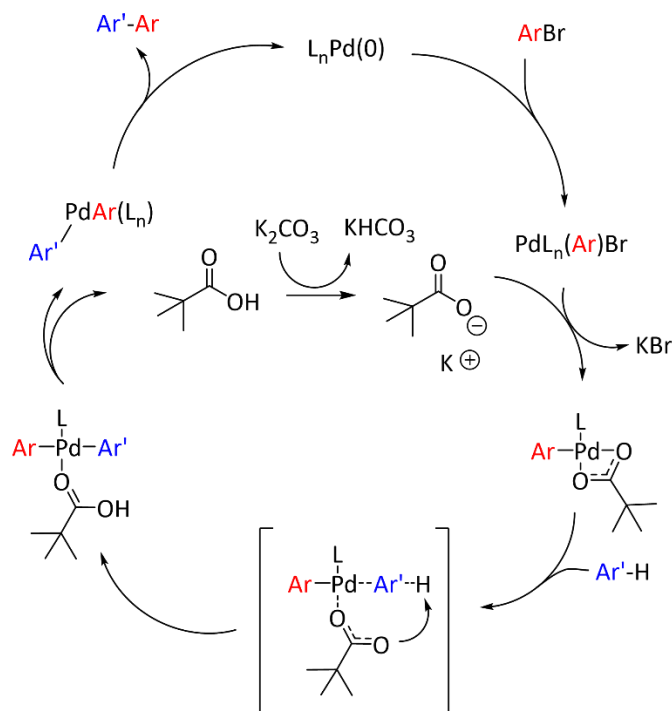


Figure 1-11. Proposed mechanism of the catalytic cycle for direct (hetero)arylation polymerisations. Redrawn from Lafrance et al.⁷¹

Since the mechanism relies on a deprotonation step, it is worth noting there may be some influence from the electron richness of the comonomers used on the efficiency of the reaction.

Beyond conventional solution polymerisation, several alternatives have been developed for the fabrication of PEDOT films. Vapour phase polymerisation, for instance, involves forming the polymer film in solution on the substrate in the presence of EDOT vapours.⁷² Alternatively, the complete absence of solvent can be achieved by oxidative chemical vapour deposition (oCVD) that negates the need for wetting/pre-treatment of the substrate surface.⁷³ More recently liquid phase depositional polymerisation has been utilised to address the moisture sensitivity, chamber limitations to substrate size and acidic side reactions found in previous techniques.⁷⁴

1.3.3 - Optoelectronics of PEDOT

PEDOT exhibits several interesting and useful optoelectronic properties. In its neutral form, if properly dispersed or dissolved, PEDOT exhibits a dark purple/blue colour. However, upon doping, the generation of polaronic and bipolaronic states at the edge of the visible and into the NIR region renders the material visually transparent. This property is of great use to a range of device physics, electrochromic and biomaterial applications.^{60,65}

Previous work has put the maximum doping level of PEDOT at 33%, 1 polaron/dopant per 3 monomer units.^{68,75,76} Not only does this give insight into the energetics and polaron binding energies of the system but it also highlights how a PEDOT backbone would in theory be saturated at a 3:1 ratio of EDOT repeat unit to styrene sulfonate repeat unit. PEDOT polymer chains typically only grow to 10s of monomer units and are often mixed with an excess (2.5+ eq.) of PSS when used in charge transport applications.¹

The charge transport properties of PEDOT:PSS can be substantially enhanced by the use of *secondary* dopants. Secondary doping should be clearly delineated from the hereto mentioned doping process, sometimes referred to as 'primary doping', that occurs in the presence of oxidants and acids such as persulfonates, poly(styrene sulfonate) etc. In secondary doping, small amounts of often polar, inert solvent molecules are added that have been shown to amplify the conductivity by orders of magnitude even to an extent beyond the removal of said dopant. Indeed, a range of solvents (DMSO, ethylene glycol (EG), DMF, methanol, ethanol etc)⁷⁷ have been investigated with the hypothesis that increases in conductivity comes from the screening of charge between the PEDOT backbone and counter-anion promoting inter-PEDOT domain connection.⁷⁶

1.3.4 - PEDOT in the biomedical sciences

1.3.4.1 - *Biocompatibility*

PEDOTs chemically inert nature in the oxidised/doped form relative to its competitors (PPy etc.) endows it with excellent electrical, chemical and thermal stability. As such, potential toxicities resulting from partial degradation pathways are less likely. PEDOT biocompatibility has been widely studied and PEDOT has demonstrated good cell viability with, for example, epithelial Hep-2,⁷⁸ fibroblasts⁷⁹ and neuroblastoma SH-SY5Y cells⁸⁰, making it an exciting material in the field of bioengineering. To make PEDOT more appropriate for use in biological systems, particularly as a scaffold material, architectures that mimic the mechanical and morphological properties of extracellular matrices are highly desired. Two such structure types are hydrogels and porous scaffolds.

1.3.4.2 - *3D porous Scaffolds*

A variety of ingenious techniques have emerged in recent years for the fabrication of 3-dimensional (3D) porous scaffold materials. Vapor phase polymerisation (VPP) has been employed wherein the monomer vapours are exposed to a scaffold template soaked in oxidant.^{81,82} Alternatively, electrochemical polymerisation can be achieved using a metal scaffold (e.g. nickel) as site of deposition.^{83,84} The most straightforward methodology, however, involves dipping a scaffold template into a solution of conjugated polymer and vacuum/oven drying to obtain a conjugated polymer-coated, conductive scaffold. For instance Ding et al. achieved just this by immersion of a melamine sponge into a PEDOT:PSS solution.⁸⁵ Despite its convenience, delamination can occur and as such crosslinking with chitosan, gelatin or collagen is often required.^{86–88}

Although impressive, the examples given above rely on fabrication in the presence of a template scaffold, an approach that can limit the conductivity as a result of blending with non-conductive materials. Usefully, techniques now exist, primarily based on orthogonal solvation, that remove the template post-fabrication through dissolution of the substrate, leaving a CP scaffold behind.^{89,90} Recent work from Wan et al. demonstrated how porous, 3D scaffolds of PEDOT:PSS could be fabricated by careful freeze-drying of an aqueous dispersion, a process known as 'ice templating'.⁹¹ The resulting structures exhibit extensive and interconnected porosity (**Figure 1-12**). This architecture was subsequently used within our research group as a scaffold in bone tissue engineering where it was demonstrated to be able to facilitate the differentiation of osteogenic precursor cells to

osteoblasts.⁹² Ice templating has been implemented in a number of systems and manipulation of experimental parameters such as sublimation/freezing rate, composition and temperature can allow control of the average pore size such that the ~100 μm scale desired for biological systems can be obtained.^{84,92}

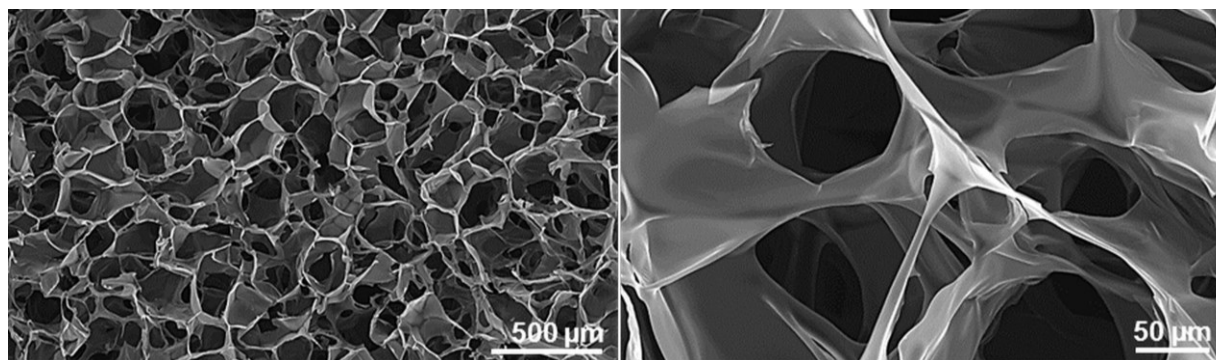


Figure 1-12. Freeze drying of PEDOT:PSS allows for the formation of porous, 3-dimensional scaffolds for bioengineering. Figure adapted from Guex et al.⁹² Adaption permitted with acknowledgement under creative commons CC-BY licence.

1.3.4.3 - Hydrogels

Hydrogels represent an exciting class of materials in biomedical sciences due to their hydrated nature and mechanical similarity to biological systems making them excellent mimics of the extracellular matrix (ECM). As with scaffolds a variety of synthetic protocols have emerged. Some authors have chosen to perform the polymerisation directly in a hydrogel substrate. Work by Xu and co-workers, for instance, soaked cross-linked carboxymethyl chitosan (CMCS) in an ammonium persulfate oxidant solution, initiating the polymerisation upon the addition of EDOT in hexane.⁹³ As shown for scaffolds, electrochemical methods, such as the formation of PEDOT hydrogels with a PVA template at low charge density, also exist.⁹⁴ Alternatively, techniques to simultaneously crosslink the hydrogel and form the polymer have been demonstrated from the mixing of a monomer/biopolymer with a oxidant/crosslinker solution.⁹⁵ In one particular study sodium periodate (NaIO_4) was used as both the oxidant *and* the crosslinker in a PEDOT/hyaluronic acid hydrogel system.⁹⁶ A final iteration sees the hydrogel precursor and crosslinker added to an already formed CP.^{97,98}

Examples of single component CP hydrogels have also begun to emerge. Systems comprised of PEDOT:PSS in the presence Fe^{3+} ions as well as non-crosslinked, amphiphilic PEDOT derivatives have successfully formed hydrogel structures.⁹⁹

Similarly, and most recently, Lu et al. developed single component PEDOT:PSS hydrogels (**Figure 1-13**) by combining the material with various concentrations of DMSO to act as a secondary dopant, followed by dry annealing and subsequent rehydration. It was observed that DMSO facilitates the formation of PEDOT:PSS nanofibrils that increase both the stability and conductivity of the subsequent hydrogel by providing a more comprehensive percolation network.¹⁰⁰

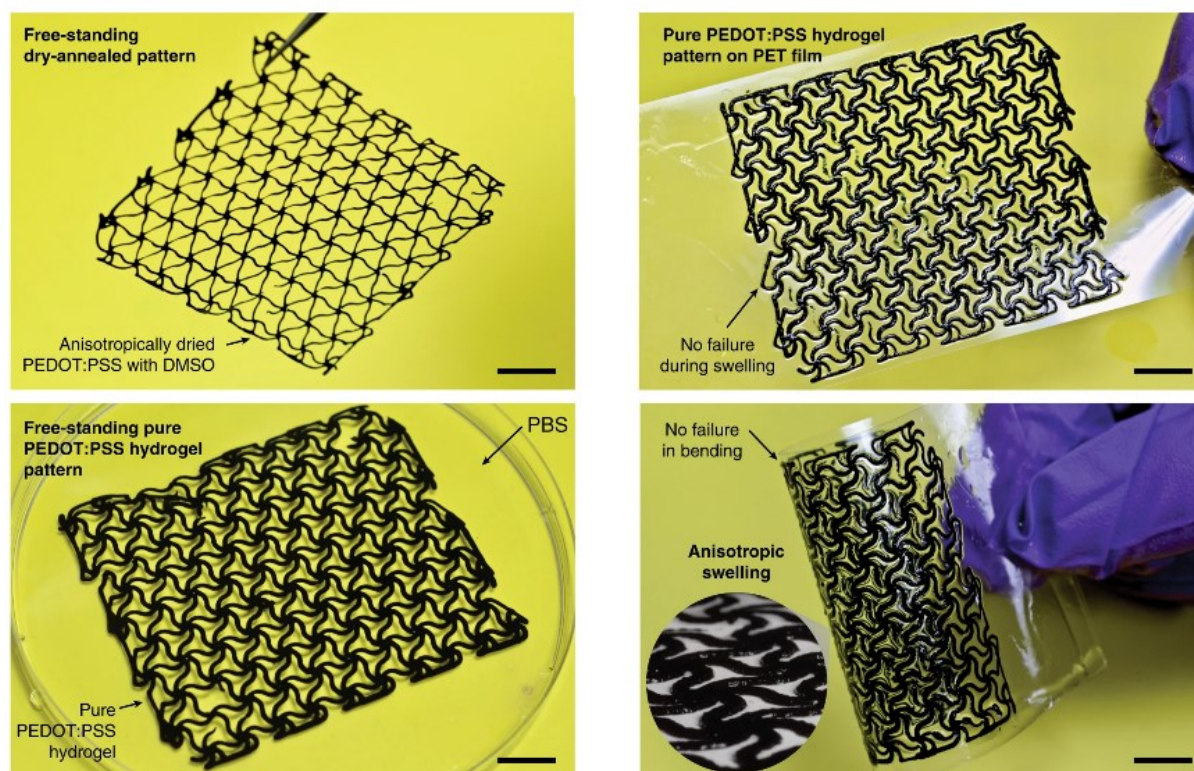


Figure 1-13. Free standing PEDOT-PSS hydrogels have been demonstrated through a dehydration/rehydration protocol with DMSO as a secondary dopant in an aqueous solution. Figure adapted from Lu et al.¹⁰⁰ Permitted with acknowledgement and link to following licence: <http://creativecommons.org/licenses/by/4.0/>.

1.3.5 - Applications

Since its inception PEDOT has found use in a diverse range of fields. The ubiquitous nature of PEDOT is too great to be exhausted here and as such the focus shall be primarily on bioelectronics applications however the interested reader is referred to various reviews for further information.^{17,30,47,101 68,102–}

105,106

1.3.5.1 - Bioelectronics

The potential uses of PEDOT systems in bioengineering have been previously described (Section 1.3.4 -) and stem from the material's remarkable chemical, electrical and thermal stability. For instance, such stability allows for the transferal of low frequency oscillating and even direct current signals to biological systems without undergoing corrosive redox chemistry as can be the case in metal electrodes.¹⁰⁵ Combined with its more biologically aligned mechanical properties, PEDOT systems make attractive materials in the interface between electronic/device architectures and tissue. Indeed, its low interfacial impedance has meant a large proportion of the literature utilises PEDOT as an interface layer between electrodes and neuronal systems.^{107,108} Ultimately, the biomaterial field's fascination with PEDOT is a culmination of its exceptional conductivity, the highest in organic polymers, its chemical stability, that permits such charge transport properties to remain stable to many and various environments, its biocompatibility and potential for derivatisation to enhance bio-integration.

Surface functionalised PEDOT films allow for enhanced bio-integration including improved cell adhesion, proliferation and differentiation. Early attempts to improve integration through functionalisation were performed using electrochemical doping methods that allowed for the physical adsorption of laminin,¹⁰⁹ nerve growth factor (NGF),⁴⁵ hyaluronic acid and heparin.¹¹⁰ Whilst improving interactions with cellular environments these large biomolecules were found to hinder both the electrochemical and mechanical integrity of the materials. As such an alternative route sees the biomolecule covalently tethered to the conjugated polymer backbone. For instance, PEDOT has been appended with a carboxylic acid moiety allowing the direct bio-conjugation of the backbone via the N-terminus of various biomolecules such as laminin. These systems were shown to improve bio-integration as well as the stability issues that plagued their non-covalent counterparts mentioned previously (**Figure 1-14**).⁴¹

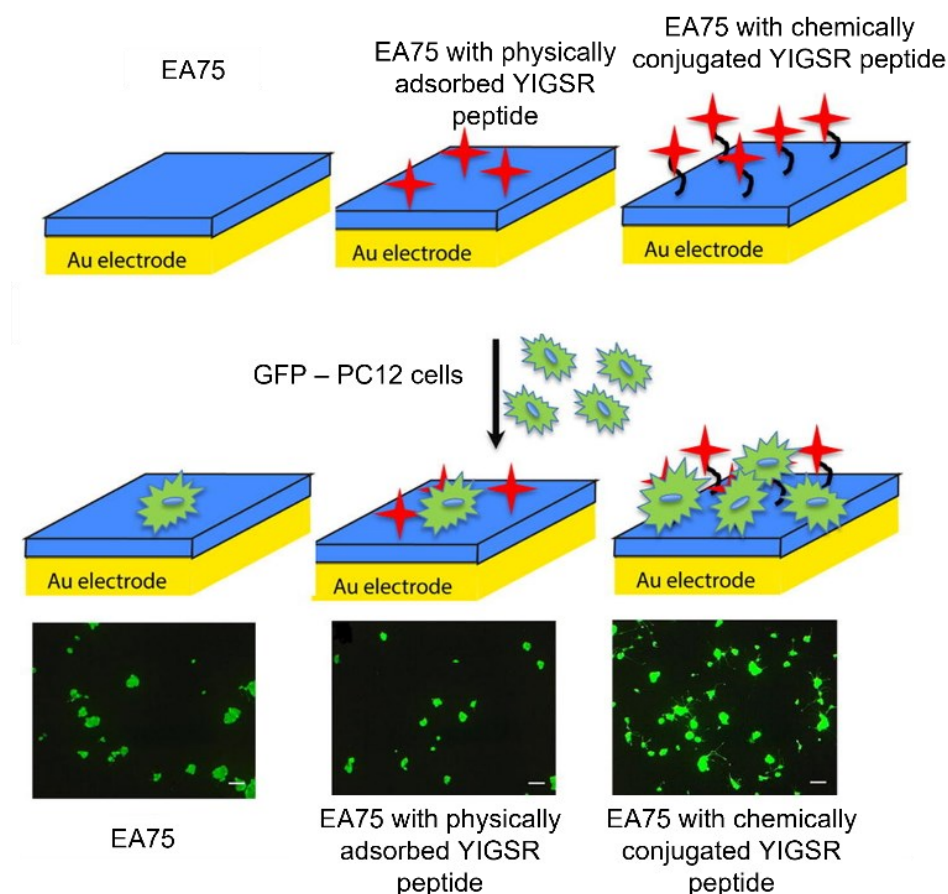


Figure 1-14. Covalent attachment of biomolecules such as the laminin-derived YIGSR peptide has been shown to greatly enhance cell attachment and proliferation. Reused with permission from Bhagwat et al.⁴¹

PEDOT has also been blended with a range of biomaterials to produce novel structures in bioengineering. Blending with biopolymers such as alginate has permitted the creation of hydrogel type systems. These architectures combine the conductive properties of PEDOT with the soft, biomimetic properties of the gels.^{94,109,111} Other blends, including with nanomaterials such as carbon nanotubes or graphene oxide, can add stability and provide electrochemically sensitive sites for the detection of substances such as neurotransmitters.^{112–114}

PEDOT based materials have also been used for drug release applications. As well as the more conventional degradation (hydrolysis)¹¹⁵ and pore size dictated release¹¹⁶, PEDOT and indeed conjugated polymers in general allow for electrically stimulated release of compounds adding an extra degree of control to the systems. Examples include the release of dexamethasone, a corticosteroid that reduces inflammation after implantation of a material/device.^{111,117} As well as releasing a range of other pharmaceuticals (tauroursodeoxycholic acid,¹¹⁸ prednisolone¹¹⁹ etc.), the ionic conductivity of PEDOT can actually allow its employment as ion channels that transport charged drug compounds from larger reservoirs, increasing the lifetime of the device.^{120,121}

It should be noted that although demonstrably biocompatible, PEDOT is a material class and therefore cannot be approved in general by the government organisations (such as the Food and Drug Administration (FDA)) but rather should be approved in the specific form (with respect to the synthesis, processing, final morphology etc.) in which it is used.¹⁰⁵ This has slowed the rate of translation and as such few PEDOT-based systems are found in the biomedical field to date. The increasingly ingenious manifestations of PEDOT for bioengineering devices found in the literature will, however, undoubtedly change this in due course.

1.3.5.2 - Other applications

When doped, PEDOT and PEDOT derivatives' polaron transitions shift into the near infra-red causing the material to become transparent. This has allowed its use as a transparent electrode in a range of devices including organic photovoltaics (OPVs), organic light emitting diodes (OLEDs) and organic field effect transistors (OFETs).¹²² Its flexibility for roll-to-roll fabrication and inexpensive fabrication sets it apart from other transparent electrode materials such as Indium Tin Oxide (ITO).^{123,124} Such inducible changes in colour/transparency as a function of oxidation state has further led to the use of PEDOT derivatives in thermochromic and electrochromic devices.^{65,125}

The ability of PEDOT to utilise the Seebeck effect to convert heat to electricity, or vice-versa, has led to its application as transparent heaters and other thermoelectric devices.¹²⁶ PEDOT can also show induced changes in morphology. PEDOT-based polymers have been shown to be able to physically expand and contract in humid environments, which has led to their use as actuators, a material type in increasing demand in the bioengineering field.¹

In recent decades, PEDOT derivatives have demonstrated themselves capable of storing large amounts of charge and, as such, have found uses in energy storage, energy conversion and supercapacitors as well as in the counter electrodes of capacitors.^{127,128} Other applications include use as an antistatic coating for photographic films as well as a coating material for cathode tube rays.⁵⁸

Clearly then, advances in the PEDOT system, or derivatives therein, would have far-reaching technological implications across a broad range of disciplines. Whilst this thesis will focus on the use of our materials in biological settings, it is anticipated that our progress could contribute to a diverse range of fields.

1.4 - Challenges in conducting polymers

1.4.1 - The problem of doping: Toward self-doped systems

So far, the conducting polymers discussed have used only external dopants. Whilst these have often taken innovative forms, such as the biomolecules themselves,¹⁷ they present several drawbacks. Firstly, external dopants, particularly small molecules, are prone to leaching from the material over time, potentially reducing charge transport properties. Secondly, a large excess of dopant is often required that can both increase the toxicity of the system and isolate the conductive polymer networks from one another, hindering charge transport. PEDOT:PSS is a prime example of this where often at least 2.5 equivalents of the dopant are used relative to PEDOT.¹

Self-doping is when the dopant is attached to the conducting polymer backbone itself. Coupling of dopants to the common conducting polymers already mentioned has been on record for some 30 years. In the case of PPy, couplings have been made to a dopant polymer to create a graft copolymer with polystyrene sulfonate (PSSA-*g*-PPY - **Figure 1-15b**). This was shown to give a conductivity on the order of 10^{-1} S/cm when in the form of a compressed pellet.¹²⁹ Alternatively, PPy has been self-doped with just a short alkyl sulfonate and used for sodium insertion/extraction in a Na-ion battery for electric energy storage (**Figure 1-15a**).¹³⁰

PANi has also seen various self-doping derivatives. Early work by Yue et al. saw the self-doped functionalisation of PANi via sulfonation give conductivities in the range of 0.1 S/cm (**Figure 1-15e**).¹³¹ Other authors have also shown the self-doping of PANi with a boronate group in the presence of phosphoric acid and fluoride (**Figure 1-15d**).¹³² A particularly intriguing example coming from Deore et al. demonstrated reversible self-doping via the complexation of D-fructose with a boronic ester-functionalised PANi.¹³³ By increasing the concentration of fluoride the saccharide could more easily complex forming an anionic ester and self-doping the system. Self-doped thiophene derivatives have also been reported in, for example, the form of benzyl or alkyl sulfonate peripheral moieties (**Figure 1-15c**).^{134,135}

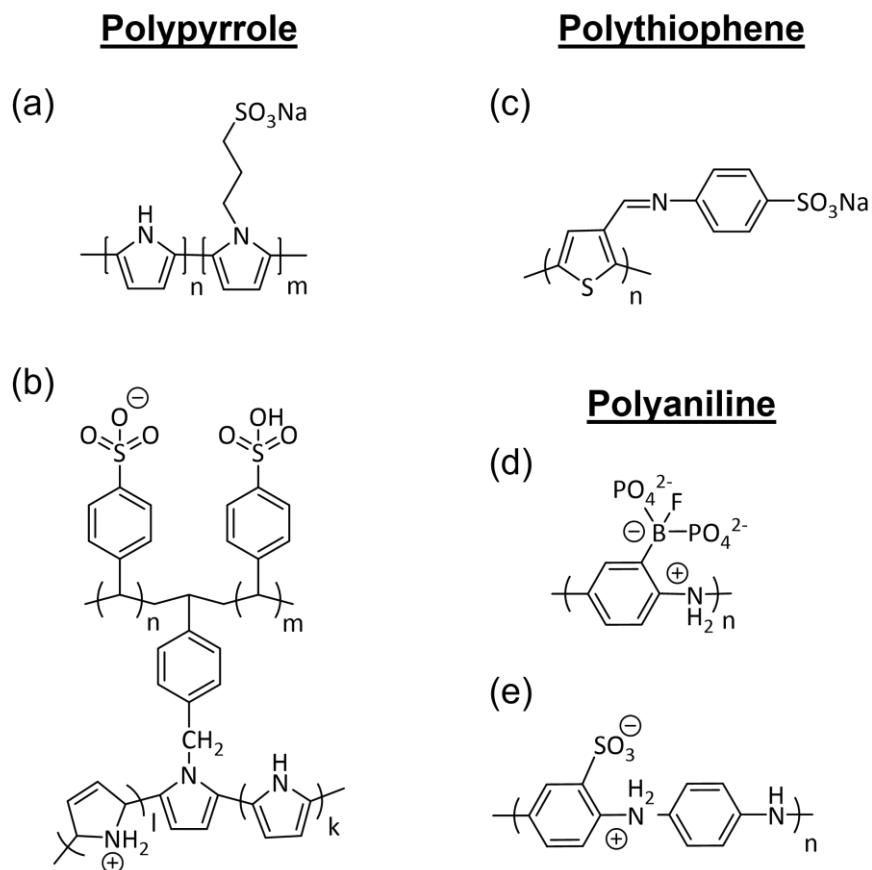


Figure 1-15. Figure illustrating self-doping of semiconducting polymers demonstrated in the literature so far for: (a), (b) – Polypyrrole; (c) - Polythiophene and; (d), (e) – Polyaniline derivatives.

These studies have not only demonstrated what is possible synthetically but also how techniques such as UV-vis, FT-IR and CV can be used to assess the degree of doping through monitoring polaron and bipolaron population change.

In the case of PEDOT, sulfonate self-doping (known as PEDOT-S – see **Figure 1-16**) has been investigated for over 20 years to improve solubility, charge transport and electrochromic capacity.^{136–138} In all cases, alkyl sulfonates have been conjugated to the periphery of the EDOT monomer, which was polymerised through a range of conditions both chemical and electrochemical. Chemical polymerisations have been primarily through oxidative pathways with the most recent example producing film conductivities greater than 1000 S/cm.¹³⁹ More recently still, however, Beaumont et al. have demonstrated the use of direct (hetero)arylation polymerisation (DHAP) to produce fully water soluble and self-doped systems from a variety of brominated and un-brominated EDOT-sulfonates and similar, with conductivities as high as 50 S/cm.¹⁴⁰ The library demonstrated therein expanded both the control and repertoire of self-doped EDOT-based systems. This thesis will look to leverage work such as this when attempting to produce more sophisticated self-doped PEDOT derivatives for biomedical applications.

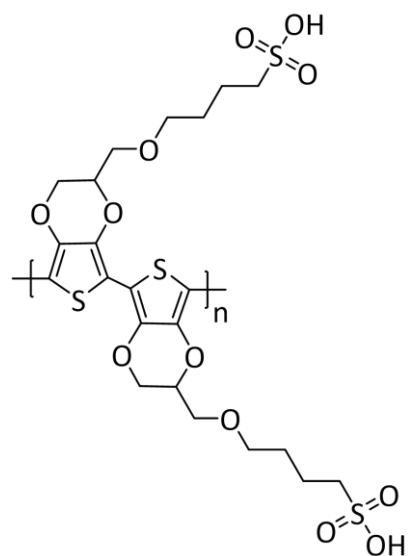


Figure 1-16. Structure of self-doped PEDOT, denoted in the literature as PEDOT-S

1.4.2 - The problem of biodegradation: Toward fully degradable conductive polymers

A prominent and prevailing issue with applying organic conjugated polymers to biomaterial requirements comes in biodegradation. It is often desirable, particularly when considering materials to be implanted or injected, that they eventually degrade to the extent that they can be excreted from the body after fulfilling their function allowing, in the case of scaffolds, full recovery and negate any need for subsequent surgery. However, the conjugated nature of CP backbones almost always renders them immune to biological degradation (hydrolysis, enzymatic, reactive oxygen species etc.) meaning such substances can persist indefinitely. Moreover, beyond use in medicinal settings, degradable materials exhibiting charge transport properties are purported to be in increasing demand for 'green', environmentally friendly 'vanishing' electronics by organisations such as ICARUS (Inbound, controlled, air-releasable, unrecoverable systems).¹⁴¹

Multiple attempts at imbuing conjugated polymer-based architectures with biodegradability by blending with degradable polymers have been documented.¹⁴² Such strategies result in what have been referred to in the literature as 'type I' materials.¹⁴¹ A recent example involved the synthesis of PANi-co-polydopamine (PDA) onto which was grafted poly(lactic acid) to be electrospun into fibres. Their structure was able to support the proliferation of cells and lose 50% of its mass after 7 weeks in an acetate buffer. It should be noted that though optoelectronic techniques were carried out for basic characterisation, no such data was supplied during the degradation that might elucidate exactly which segments of the copolymer were degrading. It might be reasonably assumed that the PANi itself may have undergone negligible degradation.¹⁴³

Though these materials appear to exhibit both conductivity and biodegradation it should be noted that in general only the portions of the material containing degradable moieties will actually be broken down and that long conjugated chains will likely endure. Whilst the amount of non-degradable material is certainly reduced the problem of degradation is not fully solved.

Considering this, another approach is to insert sites of biodegradation into the CP backbone itself, sometimes termed 'type II' materials.¹⁴¹ An early example came from the Schmidt group in 2002 wherein they reported copolymerising a pyrrole-thiophene-pyrrole trimer with adipoyl chloride to generate a partially conjugated polyester (**Figure 1-17a**). This demonstrated a conductivity in the region of 10^{-4} S/cm, could support neuroblastoma proliferation and degraded in the presence of esterase over 2 weeks.¹⁴⁴ Similar work can be found for aniline oligomers with poly(L-lactic acid) (PLLA) by Huang et al. who reported on the importance of polyester molecular weight in maintaining desired mechanical properties.^{18,145}

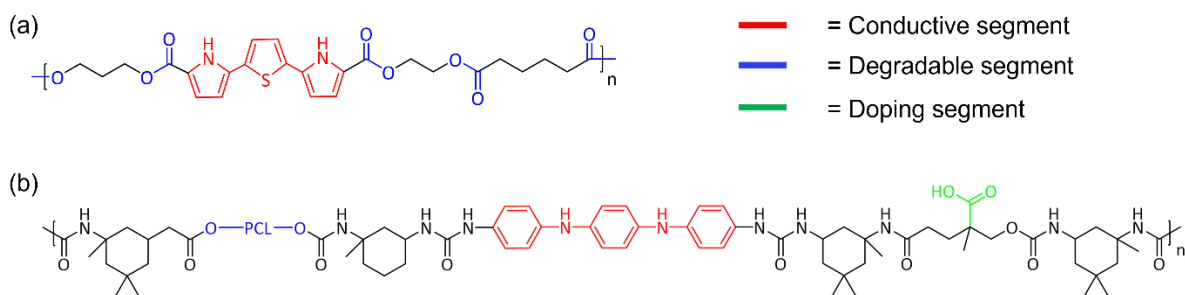


Figure 1-17. Schematics of (a) the degradable, conductive copolymer designed by Rivers et al. in 2002¹⁴⁴ and (b) the 3-component degradable, conductive and elastomeric copolymer synthesised by Xu and coworkers in 2016¹⁴⁶

To put the conductivity values achieved to date into context numerically the reader is referred to **Table 1-2** below. Though promising, many of the ‘Type II’ materials rely on oxidation with an excess of free dopant presenting both potential toxicity issues and problems with diffusion out of the structures over time. Arguably work done by Xu and coworkers has gone the furthest to address this issue by incorporating the dopant, dimethylpropionic acid (DMPA) (highlighted in green **Figure 1-17b**), directly into the polymer backbone.¹⁴⁶ As can be seen in **Figure 1-17b**, the authors were able to generate a PCL-tetraaniline-DMPA copolymer thereby linking biodegradable, conductive and doping segments respectively to form elastomeric materials. This stretchable material and its degradation products were shown to be non-toxic, supporting the proliferation of mouse 3T3 fibroblasts and displaying good biocompatibility upon *in vivo*, subcutaneous implantation with a mouse model.

As can be seen, instilling biodegradation has been predominantly achieved through incorporation of a non-conjugated, often hydrolysable linker. However, other methods that incorporate a point of scission into the conjugation itself have begun to emerge. In one example from Repenko and coworkers imidazole units were included into a backbone containing thiophene, alkyne and benzyl groups to provide a range of peroxide-degradable, fluorescent nanoparticles.¹⁴⁷ Similarly, work from Zhenan Bao’s group inserted imine moieties into a derivative of the common donor-acceptor diketopyrrolopyrrole (DPP) to give physiologically degradable, semiconductive materials capable of integration into thin film transistor device architectures with mobility values of $0.34 \text{ cm}^2/\text{V.s.}$ ¹⁴⁸

Table 1-2. Conductivity values for notable ‘type I’ and ‘type II’ degradable CPs developed to date. Rewritten from Feig et al.¹⁴¹

Material	Dopant	Conductivity (S/cm ⁻¹)	Reference
‘Type I’ materials			
PANi gelatin nanofibres	Camphorsulfonic acid (CPSA)	2.1×10^{-2}	Li 2006 ¹⁴⁹
PANi electrospun + PLCL	CPSA	1.4×10^{-2}	Jeong 2008 ¹⁵⁰
PPY with PCLF (polycaprolactone fumarate)	Anionic dopant: naphthalene-2-sulfonic acid and Na salt dodecyl benzenesulfonic acid Na salt	6×10^{-3}	Runge 2010 ¹⁵¹
PEDOT particles in PLLA	Hyaluronic acid	4.7×10^{-3}	Wang 2017 ¹⁵²
PPY nanoparticles in PDLLA	Oxidation with FeCl ₃	1×10^{-3}	Shi 2004 ¹⁵³
PPY-coated PLGA fibers	Oxidation with FeCl ₃	$R_s = 4.7 \times 10^{-5} \Omega/\text{cm}$	Lee 2009 ¹⁵⁴
‘Type II’ materials			
PANi grafted to gelatin	CPSA	4.5×10^{-4}	Li 2014 ¹⁵⁵
PPY-thiophene-PPY with aliphatic linkers	Iodine	1×10^{-4}	Rivers 2002 ¹⁴⁴
hyperbranched: aniline pentamer (AP) + PCL	Hydrochloric acid	2.4×10^{-5}	Guo 2010 ¹⁵⁶
Aniline trimer + PCL	Dimethylpropionic acid (DMPA) – in backbone	1.2×10^{-5} (dry) 4.7×10^{-3} (PBS)	Xu 2016 ¹⁴⁶
Aniline tetramer grafted to poly(ester amide)	CPSA	8×10^{-6}	Cui 2012 ¹⁵⁷
AP with PLA triblock copolymers	CPSA	5×10^{-6}	Huang 2007 ¹⁴⁵
Quaterthiophene and alkyl chains connected by ester bonds	FeCl ₃ and Fe(CIO ₄) ₃	n/a	Guimard 2009 ¹⁵⁸

Beyond the approaches for degradation mentioned thus far it is worth noting that nature already has a variety of conjugated systems with their own biochemical fragmentation pathways that can be exploited. Examples include the natural dye indigo,¹⁵⁹ the skin pigment melanin,¹⁶⁰ as well as β -carotene^{161,162} and anthraquinones.¹⁶¹

Whilst many innovative solutions have been presented to solve the problem of biodegradation in conducting systems, most still suffer from low charge transport or lack of full degradation. Further, it is surprising to note that no attempts to install degradation have been made with PEDOT, whose charge transport and stability has made it the polymer of choice for so many both in academia and industry. With all this in mind, a focus of this thesis will be the exploration of possible biodegradable yet self-doped conductive systems based on the ubiquitously utilised polymer of PEDOT itself.

1.4.3 - Supramolecular hydrogels as biodegradable alternative

All examples discussed so far have been based around conventional, covalently bound polymer systems. However, to construct systems capable of natural excretion from the body, consideration should also be given to systems constructed through predominantly non-covalent interactions. The sub-units of such architectures might already be of a molecular weight and solubility that allows for facile clearance over time *in vivo*. This is of course the domain of supramolecular chemistry.

The term supramolecular means literally ‘beyond’ the molecule and is the science of controlling and understanding primarily non-covalent intermolecular interactions that yield specific desirable conformations. Supramolecular systems leverage electrostatic, pi-pi stacking, van der Waals as well as hydrophobic interactions to self-assemble into highly ordered and well-defined architectures. This can be between just two constituents, such as a host-guest system, or billions in the case of membrane formation and nanowire assembly. Famous examples of supramolecular chemistry include, but are certainly not limited to, molecular cages,¹⁶³ physically bonded knots¹⁶⁴ and motors,¹⁶⁵ nanowires/fibrils,¹⁶⁶ nanofractals,¹⁶⁷ template directed synthesis¹⁶⁸ and supramolecular gels.¹⁶⁹

To be relevant in the field of biomedicine, however, self-assembled systems must be aqueous based and biocompatible. Whilst many examples utilising supramolecular architectures exist in bioengineering (e.g. micelles, liposomes and polymersomes), for scaffold applications the controlled assembly of peptide-based small molecules, commonly termed low molecular weight gelators (LMWGs), into hydrogels is ideal. Such hydrogels are biocompatible, mechano-compatible and highly modular with the potential to add bio-functionality through epitope appendage.

In brief, LMWGs take inspiration from nature by utilising short peptide sequences that can readily self-assemble into larger, ordered microstructures. Early work into peptide fragments responsible for amyloid formation identified aromatic amino acids like phenylalanine as promoting ordered aggregation.^{170,171} Since then, phenylalanine-based di- and tri- peptide sequences have been shown to self-assemble into nano-fibres that subsequently entangle allowing the construction of hydrogels.^{172–174} Indeed substantial efforts have been made to map the design space of di- and tri- peptide sequences using both experimental and coarse grained modelling. Here it was again demonstrated that those with the greatest aggregation propensity (AP), a prerequisite to self-assembly, contain aromatic amino acids such as phenylalanine and tryptophan.^{175,176} Such is the self-assembling propensity of phenylalanine, as dictated by the combination of π -stacking and hydrogen bonding, that it has even been reported with just the single amino acid.¹⁷⁷

The identity of the group found capping the, most commonly, N-terminus has also been shown to have substantial implications as to the assembly ability of the peptide derivatives. As with the peptide sequence itself, aromatic capping groups most commonly favour aggregation and self-assembly in aqueous systems. Notable examples include appendage of carbazole,¹⁷⁸ fluorene,¹⁷⁹ pyrene,¹⁷³ naphthalene,^{172,180} anthracene and phenanthrene moieties and derivatives.¹⁷³ Heterocyclic examples also exist in the literature that exploit additional hydrogen bonding from the capping group itself. For instance, a range of examples come from indole,^{181,182} phenothiazine¹⁷⁹ and spiropyran¹⁸³ derived systems. These can provide desirable additional intermolecular interactions such as an extra site of hydrogen bonding for improved mechanical properties.

The formation of 1-dimensional fibres is often not assumed to be the thermodynamic minimum of the system and indeed is suggested to represent a kinetically trapped state that arises in the inhibition of crystallisation or precipitation, the true energetic minimum.¹⁶⁹ As such careful consideration of the process by which the gels are formed is crucial since such dramatic variation in properties and morphology can be observed from the same LMWG. Of particular importance is the method of gelation. Typically, gelation is brought about by some reduction in the solvation of the LMWG in its medium. This can be brought about by a pH switch, heat trigger,¹⁸⁴ solvent polarity switch,¹⁸⁵ a salt trigger (such as Ca^{2+})¹⁸⁶, a chemical reaction (e.g. disulphide reduction)¹⁸⁷ or some kind of enzymatic pathway.¹⁸⁸

The choice of method will determine both the final properties and the reproducibility of those properties, often as a result of kinetic control or lack thereof. For instance, pH switching can be achieved either by a sudden change, such as the addition of HCl to a mildly basic LMWG solution, or by a gradual one, such as the slow hydrolysis of glucono- δ -lactone (GdL) pioneered by the Adams

group.¹⁶⁹ The latter of these has been shown to give more reproducible final hydrogels exhibiting properties of a smaller standard deviation.

In all, peptide LMWG hydrogel systems increasingly offer a viable alternative to traditional, polymeric hydrogel systems in the field of bioengineering. Their non-covalent nature provides an innate biodegradability whilst the use of amino acids naturally found in the body infers biocompatibility and tuneable bioactivity. A wealth of studies already exist that demonstrate non-cytotoxicity at and above gelation concentrations.^{178,180,189,190} Given the advantages laid out above, this thesis will explore not only covalently linked but also supramolecular designs to create degradable and conductive polymeric systems. By mapping out the design space somewhat for oligo-EDOT-based self-assembling peptides, a potentially more elegant charge transporting biomaterial solution might be presented.

1.5 - Thesis Aims

As has been outlined here, a number of challenges and opportunities are still present in the design and applications of conductive organic electronics. Here they will be briefly discussed in the context of the aims of this thesis.

Regarding the issue of biodegradation highlighted above, in chapter 2 efforts towards the creation of a fully biodegradable derivative of PEDOT:PSS will be presented. The aim will be to demonstrate both proof of concept as well as potential integration and biocompatibility when placed in a biological context. In this vein of work the thesis ultimately aims to install self-doping into the system, a feature that is almost always absent from type II biodegradable polymers to date.¹⁴¹

For the issue of self-doping and functionality in PEDOT derivatives, there is still extensive scope to expand and tailor PEDOT materials properties to interface with biological systems more appropriately. In Chapter 3 possible useful PEDOT derivations will be explored, primarily through side chain chemistry modifications, and their applications to the biomedical sciences assessed.

Another aim of this thesis is to investigate supramolecular oligo-EDOT-based alternatives that might address the issues of biodegradation and biocompatibility as well as expand the current oligo-EDOT approaches to biomedical solutions to include well-defined hydrogel systems. The self-assembly system chosen and discussed in Chapter 4 will be derived from the well-established low molecular weight gelator (LMWG) field. Links between molecular design and material properties will be examined on the mono-EDOT scale and used to rationalise the design of longer oligomers.

Finally, in Chapter 5 organic semiconducting polymer and supramolecular chemistry are brought together through elucidation of a novel form of fractal self-assembly. The applications of such a system may fall more in the field of semiconducting devices than biomedical sciences but still represent the exploration of self-assembling semiconductors. Indeed, these may well have future utility in bioengineering since they mimic the dendritic assembly of charge carrying tissue types such as neurons and as such may form more complex material-tissue interfaces.

Chapter 2 - Degradable, conductive polymers for biomedical applications

2.1 - Introduction

A major drawback of conductive polymers is their lack of degradability. If these materials are designed to function *in vivo* for defined periods of time, such as required for a scaffold, biodegradation into non-toxic and easily excretable products is highly desirable to encourage tissue repair and negate removal surgeries. Unfortunately, the conjugated nature of conductive polymer backbones renders them generally inert to cleavage through mechanisms available in the biological milieu. This highlights an inherent tension present in this field from the outset: installation of degradable conjugation breakers is required for degradation but will in turn disrupt charge transport. Materials that are able to overcome this and function with a higher level of complexity are thus highly desirable. Since poly(3,4-ethylenedioxythiophene) (PEDOT) is the gold standard in conducting organic polymeric systems, a degradable derivative of this system is of particular interest not just to the biomedical fields but also to any area where temporary, degradable electronics might be desired. This chapter focuses on the design and synthesis of several versions of a degradable and conductive PEDOT derivatives. The polymers are characterised, with the challenges and subsequent design/synthesis alterations discussed.

2.2 - Background

As outlined in chapter 1, systems incorporating conjugation breakers have been referred to as ‘type II’ degradable conductive polymers and are more completely degradable than ‘type I’ where CPs are simply combined with degradable biomolecules.¹⁴¹ The examples produced to date, whilst encouraging, often exhibit relatively low conductivities ($<10^{-3}$ S/cm) and are frequently not processed into morphologies relevant to biomaterials. Furthermore, whilst a number of fully degradable systems have been documented, most do not include a self-doping component and as such their charge carrier performance may be unstable and any dopant that is used may prove cytotoxic.

Since the state of the field as a whole has been outlined thoroughly in Chapter 1, only comments on direct PEDOT derivatives are mentioned here. ‘Type I’, polymer composite examples have been shown for PEDOT-based systems. In one example a biodegradable PEDOT/carboxymethyl chitosan composite hydrogel was demonstrated as a viable scaffold for PC12 cells.¹⁹¹ In another study, a graft PEDOT/poly(l-lactic acid) polymer was shown that lost 80% of its mass after hydrolytic degradation for 120 days.¹⁹² As with all ‘type I’ materials the obvious limitation in both is the non-degradable PEDOT segment, so this approach would not achieve the goals of the current chapter. Furthermore, the examples do not include a dopant and as such can likely not guarantee high or consistent conductivity.

Degradation attempts have been made on PEDOT:PSS itself. A recent study showed how PEDOT:PSS could be degraded by hydrogen peroxide in the presence of iron(II) chloride.¹⁹³ Though interesting, the utility of this material *in vivo* is limited given the specificity of the conditions. Further, the system still suffers from the same problems of a system without self-doping e.g. dopant leaching, toxicity etc.

Beyond those, or others very similar to those, mentioned above, little has been demonstrated in the way of degradation in PEDOT and as such the research space for a fully degradable, conductive PEDOT derivative is currently, to the best of our knowledge, unexplored. This chapter will therefore outline several designs created to fill this gap, with the evolution between them explained.

2.3 - Results and Discussion

Throughout this work a plethora of different synthetic strategies were investigated in order to render a PEDOT derivative biodegradable. In this chapter two such designs, denoted design 1.0 and design 2.0, are presented in detail and the evolution from one to the other outlined.

2.3.1 - Design 1.0 – Polycondensation

The first milestone of the work was to design and synthesise a polymeric system that incorporates both the oligo-EDOT backbone and conjugation breaking points of degradation. Hence a discussion of the synthesis is first required.

2.3.1.1 - Synthesis

Initial work to create degradable conductive polymers utilised chemistry developed by Spicer et al. in which EDOT oligomers were easily capped with a variety of functional handles. In brief, EDOT monomers could be coupled to a range of nucleophiles via oxalyl chloride (**Figure 2-1a**). Subsequent successive brominations and direct arylations could then allow mono- or di-capped oligomers, up to heptamers, to be readily prepared (**Figure 2-1b**).¹⁹⁴

Considering this, a variety of avenues were attempted based around installing either alcohols and/or carboxylic acid capping groups. Given the simplicity of the chemistry and lack of difficult-to-purify reagents, such as metal catalysts, Fischer esterification was identified as a promising route to degradable conjugated polymer synthesis. This would require the installation of carboxyl and hydroxy groups to either end of an EDOT-oligomer. Initial designs involved constructing a single oligomer bearing both the alcohol and carboxylic acid (**Figure 2-1c** - bottom). However, latter stages in this synthesis were fraught with extensive solubility issues: the carboxylic acid did not provide sufficient water solubility, precluding reverse phase purification etc., whilst the rigid oligomer caused precipitation in most organic solvents. Multiple iterations ensued including attempts to construct co-monomers both capped either with alcohols or carboxyl moieties (**Figure 2-1c** - top) however in most cases solubility again became prohibitive when attempting to make trimeric species.

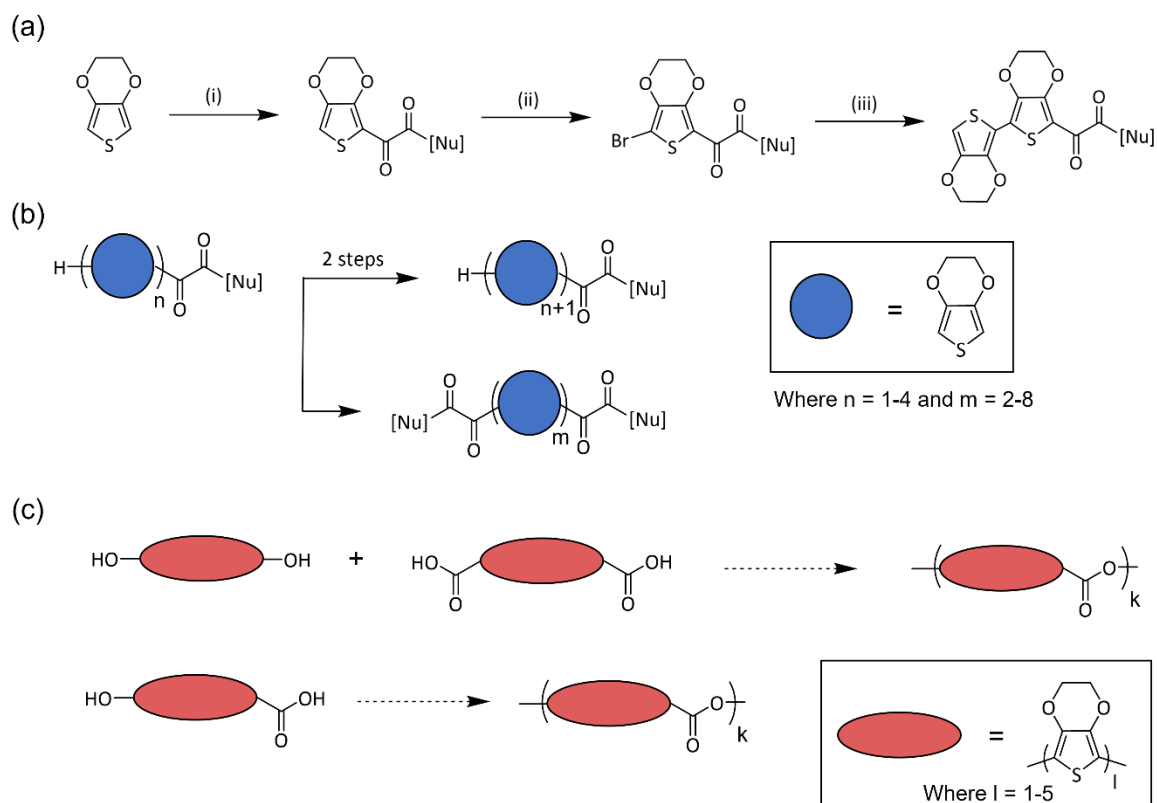


Figure 2-1. (a) An outline of the main chemistry demonstrated by Spicer et al. to derivatise EDOT.¹⁹⁴ Conditions: (i) Oxalyl chloride, dioxane, 1 hour at 100 °C, then triethylamine and requisite nucleophile 2 hours at room temperature (ii) N-bromosuccinimide, THF, acetic acid, 2 hours at room temperature (iii) palladium(II) acetate, pivalic acid, EDOT, potassium carbonate and DMF, 2 hours at 90 °C; (b) an illustration of how larger oligomers both mono- and di-capped could be built up through this chemistry (note the 2 steps are (ii) and (iii)); (c) schematic illustrating the different approaches investigated in designing and synthesising a degradable PEDOT derivative.

Ultimately, it was the incorporation of highly soluble 3,4-propylenedioxythiophene (ProDOT) derivatives from Ponder et al.⁶⁵ that finally allowed for an appropriate di-acid to be synthesised. As shown in **Scheme 2-1**, this was achieved by first synthesising a dibromo ProDOT derivative (**1**) from commercially available 3,4-dimethoxythiophene. Nucleophilic substitution then afforded ProDOTs grafted with solubilising groups, either alkyl (2-hexyldecyl (HD) – R₁) or alkoxy (triethylene glycol monomethyl ether (TEGME) – R₂), (**2a**, **2b**) that could be subsequently inserted between a capped and brominated EDOT derivative (**4**) via standard direct arylation chemistry yielding **5a**. Synthesis of **5b** was met with extensive purification issues and indeed success was only found when combining both steps in one pot to give **6b** after reverse phase chromatography. In the case of **5a**, deprotection then gave the corresponding di-acid (**6a**) that could be readily copolymerised via polycondensation using

Soxhlet extraction and 4 Å molecular sieves such that the refluxing toluene would be dehydrated throughout the reaction, pushing the equilibrium toward polyester formation. The elegance of this final step was its simplicity since it only required the comonomers to be dissolved in toluene and refluxed without even the need for a catalyst, making subsequent purification facile. This synthetic method was successfully achieved in the case of **7a** and **7b** where the long hexyldecyl side chains provided sufficient solubility to allow dissolution in toluene. The two co-monomers chosen in this case, 1,8-octanediol (OD) and triethylene glycol (TEG), were initially selected in order to probe how more or less hydrophilicity might impact access of water to the oxalyl ester and hence degradation. Pleasingly, this produced polymers with estimated molecular weights up to 244 kDa when compared to a poly(methyl methacrylate) (PMMA) standard. This is notable as an exceptionally high molecular weight polymer system that required no catalyst and hence simple purification. A third polymer was attempted with both the TEGME side chains and TEG comonomer (**7c**) as the most hydrophilic, and hopefully fastest degrading, example. Unfortunately, the di-acid **6b** could not be dissolved in toluene even at refluxing temperatures, preventing polymerisation. To tackle this problem, polymerisation was attempted using the protected monomer **5b** with an acid catalyst as a poly-transesterification. A commonly used choice is *p*-toluenesulfonic acid (pTSA),¹⁹⁵ however matrix assisted laser desorption/ionisation time of flight mass spectroscopy (MALDI-ToF) indicated molecular weights only up to around 4 kDa were produced, suggesting possible steric hinderance around the oxalyl ether was limiting polymerisation.

Attempts to synthesise the third derivative, EPE(TGME)-*co*-TG (**7c**), are ongoing, nonetheless two oligoEDOT polyesters were successfully fabricated: EPE(HD)-*co*-C8 (**7a**) and EPE(HD)-*co*-TG (**7b**) as shown below in **Figure 2-2**.

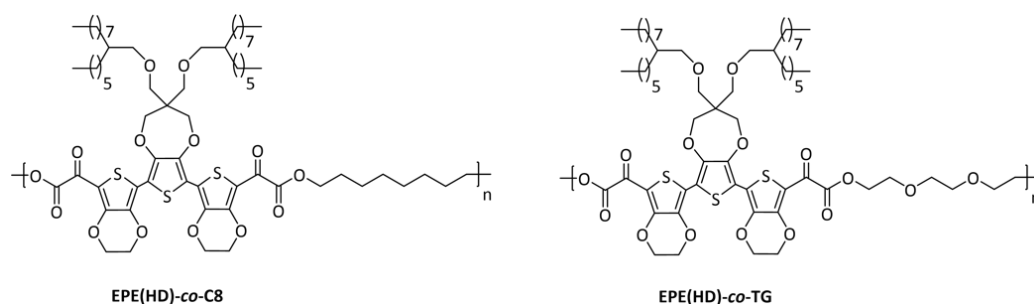
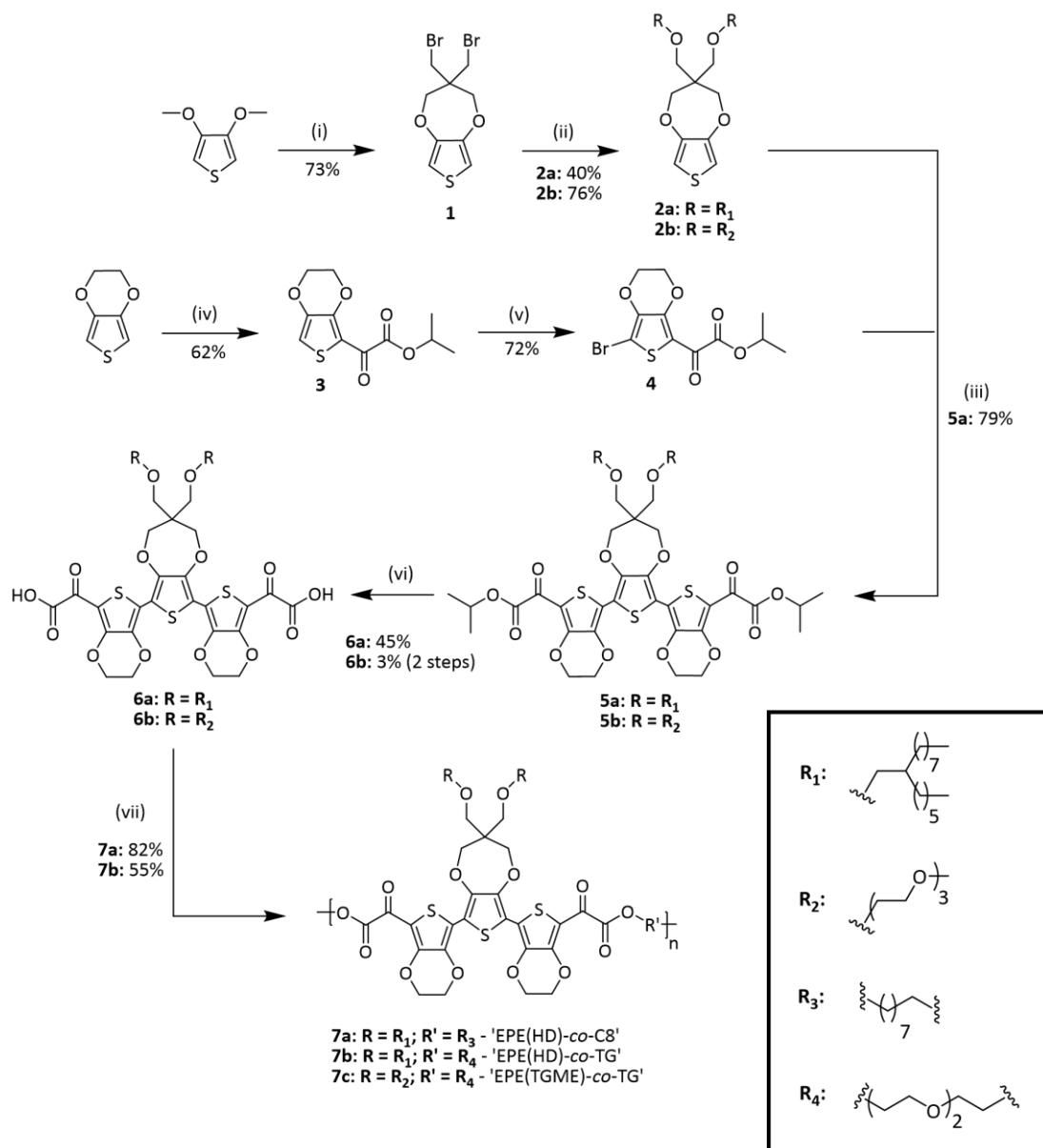


Figure 2-2. Schematic of the two polymers successfully synthesised

The absence of any catalyst meant the entire content of the reaction was simply a range of molecular weights for the desired polymer. GPC indicated even before dialysis purification in THF, the reaction

crudes contained primarily excellent molecular weights over 200 kDa with dispersity indices ($\bar{M}_w/\bar{M}_n$) down to 1.5.



Scheme 2-1. Synthetic route used in production of PEDOT-based polyesters. Conditions: (i) p-toluene sulfonic acid, toluene, reflux, 18 hours; (ii) NaH, HO-R, DMF at 110 °C for 18 hours; (iii) Pd(OAc)₂, pivalic acid, K₂CO₃, DMF at 90° for 3 hours; (iv) oxalyl chloride at 100 °C for 1 hour, isopropanol, triethylamine at room temperature for 2 hours; (v) NBS, THF, acetic acid, room temperature for 2 hours; (vi) THF, NaOH, H₂O, room temperature for 2 hours; (vii) HO-R'-OH, Toluene, reflux for 3 days.

2.3.1.2 - Polymer characterisation

To investigate the doping of the polymers, different ratios of methanesulfonic acid were added to each polyester and probed with UV-visible spectroscopy (UV-vis) (**Figure 2-3a** and **b** - top). For both polymers a shoulder appears at approximately 550 nm as the concentration of acid is increased. However, whilst EPE(HD)-co-TG shows the gradual appearance of a band near the infrared (beyond 800 nm), such a band appears to already exist for EPE(HD)-co-C8 prior to doping suggesting possible doping in ambient conditions. One possible route would be through an acid-doping mechanism from water in the air acting as a mild Bronsted-lowry acid which involves use of a nearby polymer chain as an oxidant.¹⁹⁶ It should be noted the process of acid-doping is still under debate. Further application of excess acid resulted in complete shifting of the main peak for EPE(HD)-co-TG from 470 to 540 nm and appearance of new peaks at 550 and 600 nm for EPE(HD)-co-C8.

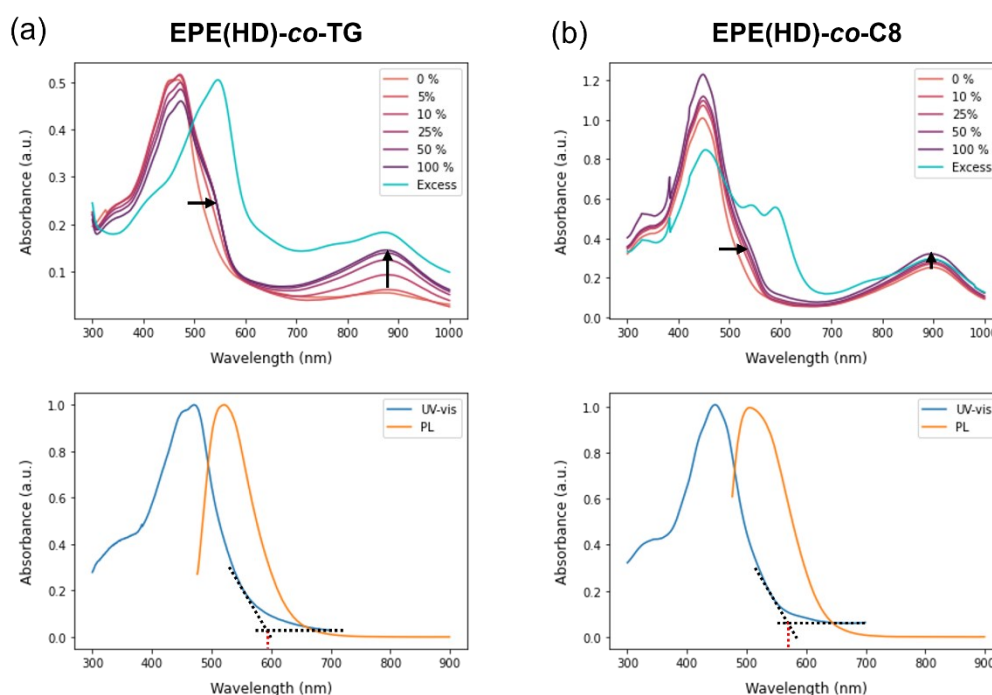


Figure 2-3. Absorption data of the polymers with addition of methane sulfonic acid (top) and photoluminescence (PL) superimposed on UV-vis spectra (bottom) for (a) EPE(HD)-co-TG and (b) EPE(HD)-co-C8 respectively.

Interpretations in the literature over the identity of the peaks seen in polythiophene derivatives such as PEDOT can differ substantially, particularly between pre- and post- the development and use of DFT.¹⁹⁷ Given reports that tosylate oxidants in conventional oxidative polymerisations give pristine

samples doped up to 33% (1 dopant every 3 EDOT units) and that increasing still further becomes energetically prohibitive¹⁹⁸, it is unclear if our trimeric system could be oxidised beyond a +1e polaronic state by acid alone. This could implicate the 590 nm shoulder as a full band gap transition in the +1e oxidised state (P2 of **Figure 2-4**) whilst the emerging near-IR (800-1000 nm) peak represents a transition to a polaron state in the band gap (P1 of **Figure 2-4**).

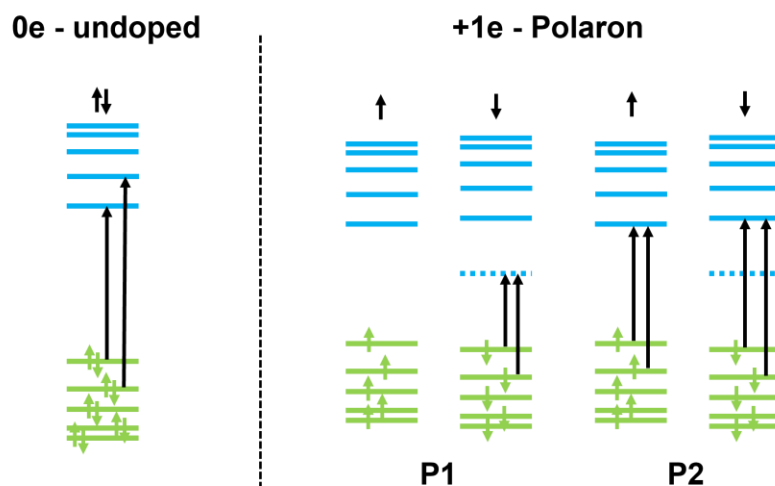


Figure 2-4. Schematic illustrating possible transitions resulting in the UV-vis spectra obtained. This interpretation is redrawn from Zozoulenko et al.¹⁹⁷ in which PEDOT transitions are modelled using DFT. In the polaronic case the diagram is divided by spin to illustrate the asymmetry in absorption assuming, arbitrarily, accommodation of only down spin particles to a state in the band gap (P1, right).

The additional peaks seen with excess acid addition in EPE(HD)-*co*-C8 implying further polaronic/bipolaronic states are curiously absent from the EPE(HD)-*co*-TG. However, insufficient data is present to assign transitions to such a detailed absorption landscape.

Using the CV data, **Figure 2-5a**, estimations could be made of the HOMO level by comparing the onset of oxidation to that of ferrocene using the following equation.¹⁹⁹

$$E_{HOMO} = -e(E_{ox}^{onset} + 4.8) \quad (\text{Eq. 2-1})$$

Where E_{ox}^{onset} is obtained vs ferrocene and 4.8 is the number of eV ferrocenes HOMO level is below vacuum. Similarly, the absorption spectra (as shown in **Figure 2-3a** and **b**) can be used to estimate the band gap, E_g , using.

$$E_g = hc/\lambda_{onset} \quad (\text{Eq. 2-2})$$

Where h is Plank's constant, c is the speed of light and λ_{onset} is the onset wavelength of absorption. By combining these, a picture of the energetic landscape for the polymers can be created. As shown in **Figure 2-5b**, band gaps not dissimilar to PEDOT are achieved albeit at a slightly shallower states relative to vacuum. Qualitatively this can be understood through the shorter conjugation length providing, for instance, less space for a charged state to 'spread out' and be stabilised – a rough analogy could be a 'particle in a box' with a shorter length. Nonetheless, the data implies band gaps within 0.2 eV and HOMO levels within 0.3 eV of PEDOT, a difference that should not prevent adequate charge transport for biomedical purposes.

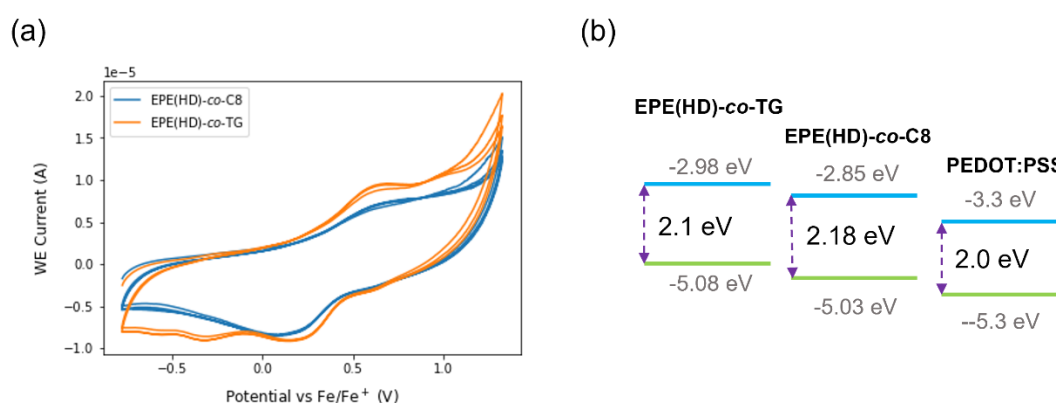


Figure 2-5. (a) Cyclic voltammetry (CV) of the two polymers and; (b) their estimated energy diagrams with PEDOT:PSS for comparison. Data for PEDOT:PSS taken from Ahn et al.²⁰⁰

2.3.1.3 - Conductivity

Thin films of the polymers proved difficult to fabricate owing to their unusual lipophilicity particularly in the case of EPE(HD)-co-TG. Conventional spin coating resulted in 'coffee stained', uneven films regardless of spin cycle, solvent, concentration, substrate type and amount used. Instead, immersion of glass substrates in a solution of the polymer overnight resulted in more acceptable thin film formation.

Unfortunately, the films obtained, particularly when methanesulfonic acid was included as a dopant, were still inhomogeneous, limiting the accuracy of any conductivity estimates. That being said, in the doped state the materials appeared to exhibit estimated conductivities in the range of 10^{-4} - 10^{-2} S/cm. For context this would place it at the upper end of both 'type I' (blended systems – only partially degradable) and 'type II' (conjugation breaking systems – completely degradable) degradable conducting polymers.¹⁴¹ Efforts are ongoing to establish more reliable conductivity values for these polymers.

2.3.1.4 - Degradation experiments

Assessment of degradation requires careful consideration. Whilst many publications chose to adopt a simple mass change approach of a solid in solution, this approach was found to be difficult to interpret given the small masses available and the potential that delamination could be misinterpreted as degradation. Instead, it was initially opted to assess degradation using gel permeation chromatography to get a better picture of chain scission and decouple this from processes such as delamination. Unfortunately, none of the degradation experiments indicated any degradation for the hydrophobic EPE(HD)-co-C8 and so most of the data presented here will be of EPE(HD)-co-TG which, unsurprisingly given its greater hydrophilicity, showed some moderate evidence of cleavage.

Efforts were initially made to degrade the systems using 1M NaOH as an accelerated test of hydrolysis that could occur *in vivo*. Unfortunately, after 2 weeks even in the case of EPE(HD)-co-TG no difference was seen in the GPC trace as shown in **Figure 2-6a**. Since oxalyl ester linkers have been shown conclusively to degrade by hydroxide (Appendix II - **Figure A 1**), it was thought the polymer was simply too hydrophobic, preventing the diffusion of hydroxide into the backbone to instigate degradation. The materials were therefore solubilised in DMF (0.5 ml) and mixed with 1M NaOH (0.5 ml), however no degradation was again observed (data not shown). At this point, degradation was assessed not only in hydroxide as a hydrolysis process but also in 3M peroxide (0.5 ml) given literature precedent of peroxalate degradation through such reactive oxygen species, the like of which are found in macrophage digestion pathways.^{201,202} Whilst again EPE(HD)-co-C8 showed no obvious change in GPC trace (**Figure 2-6c**), EPE(HD)-co-TG showed a complete erasure of the polymer peak indicating successful backbone scission. These results were interpreted cautiously however since artefacts were later found whereby the polymers occasionally appeared to be salted out of the DMF solution, albeit inconsistently, by the residual ions from degradation experiments when prepared for GPC erroneously indicating degradation. In planned future experiments this will be tackled through desalting

techniques, such as short desalting size exclusion cartridges to remove excess salts, when preparing samples for GPC.

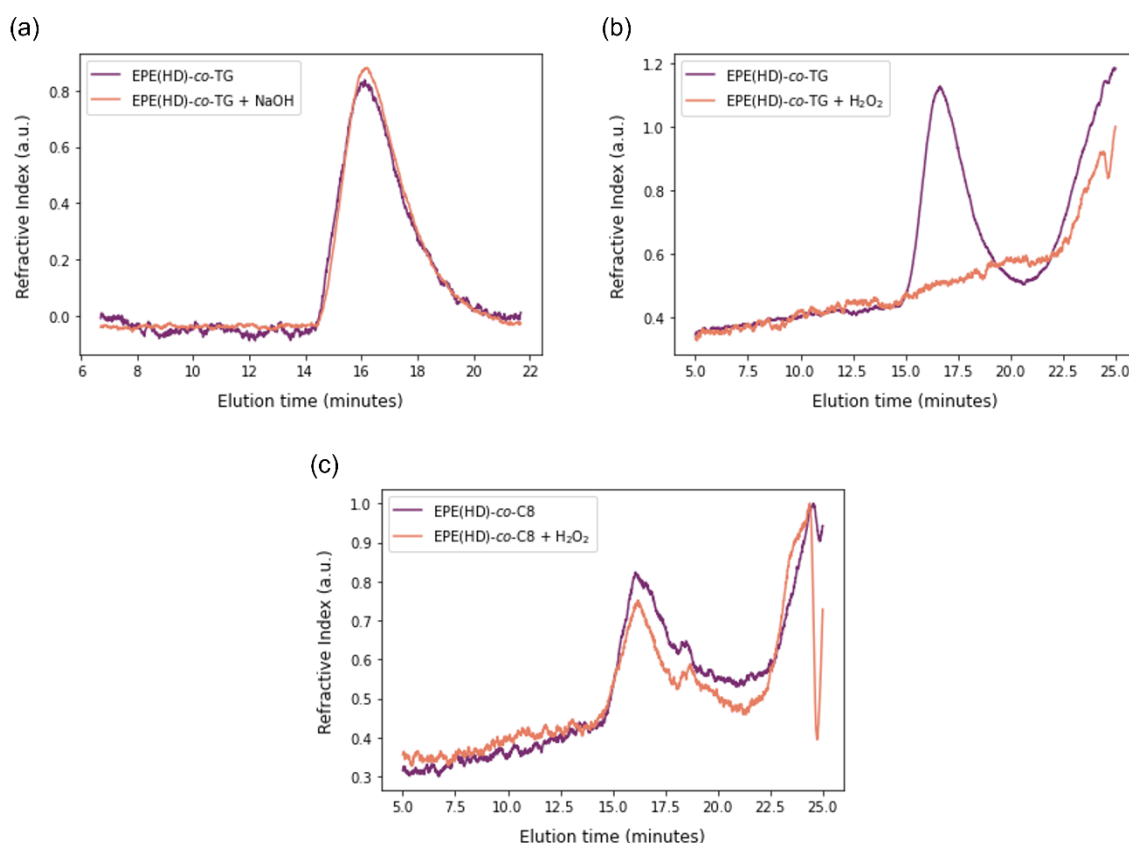


Figure 2-6. GPC traces comparing (a) before and 2 weeks after addition of 1M NaOH to EPE(HD)-co-TG as a solid deposit in a glass vial; (b) before and 2 weeks after addition of H₂O₂ to EPE(HD)-co-TG dissolved in DMF; and (c) before and 2 weeks after addition of H₂O₂ to EPE(HD)-co-C8 dissolved in DMF.

It was deemed that complementary analysis was required to assess degradation. Formation of nanoparticles (NPs) from semiconducting polymers through nano-precipitation is commonly employed and it was reasoned this might also provide a route to examine degradation effects. Pleasingly, formation of NPs was readily achieved with dynamic light scattering (DLS) indicating aggregates of around 75 and 50 nm diameter for EPE(HD)-co-C8 and EPE(HD)-co-TG respectively (**Figure 2-7a-c** – H₂O data). Curiously, incubation of the NPs with 1M NaOH revealed a dramatic increase in particle diameter (**Figure 2-7a**). It was speculated this might be a result of instability in ionic salt solutions and as such NaCl controls were prepared (**Figure 2-7c**); however, only a slight

increase in hydrodynamic diameter was observed. The increase in diameter implies decreasing stability in solution but is unlikely to come from degradation since the monomers are far more soluble in water than the polymer, particularly in basic conditions. One possibility could be hydroxide-mediated de-doping of the sample, removing polarons generated in ambient conditions, reducing the charge and therefore aqueous solubility of the polymers thereby inducing greater aggregation. Spectroscopy techniques would be required to properly elucidate this shift in energetic populations.

When incubated with hydrogen peroxide (**Figure 2-7b**), although little difference was seen in the case of EPE(HD)-co-C8, a decrease in particle diameter of around 20 nm and loss of higher diameter tailing (highlighted in **Figure 2-7**) is observed for EPE(HD)-co-TG after 4 days implying possible degradation. This is consistent with the previously discussed GPC data suggesting cleavage of EPE(HD)-co-TG in the presence of peroxide indicating the inclusion of a triethylene glycol comonomer provides enough hydrophilicity to allow peroxide-mediated cleavage.

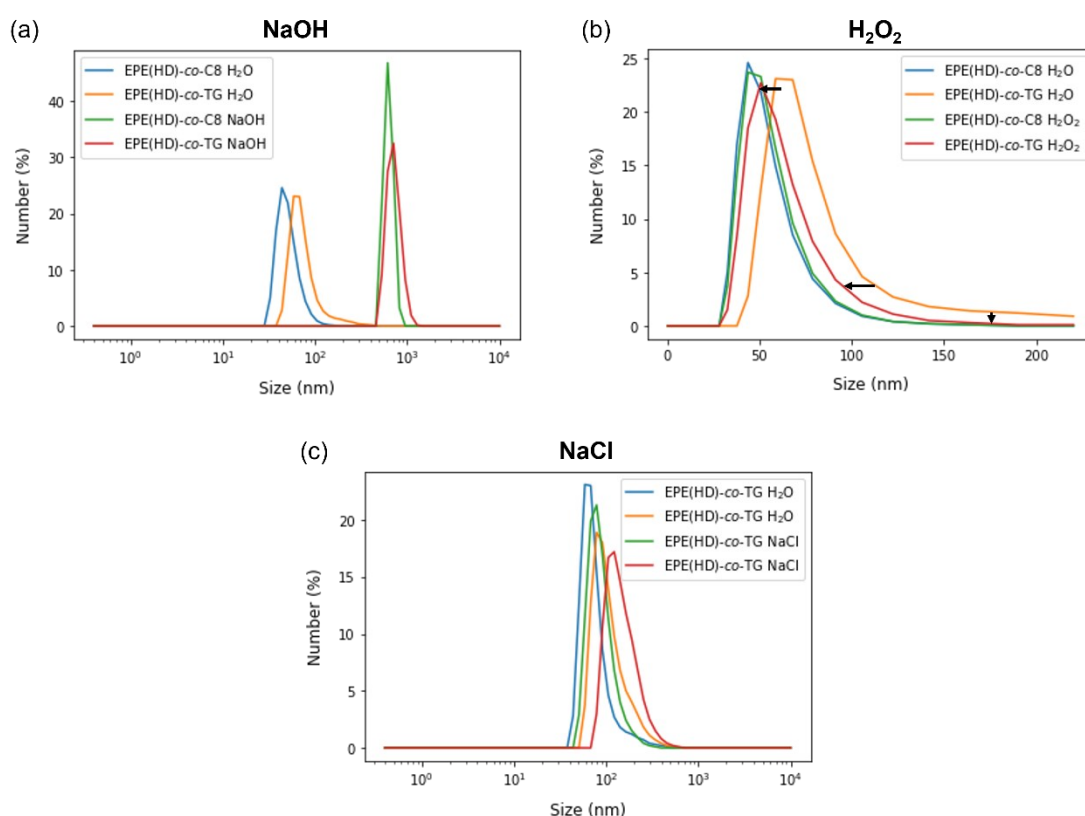


Figure 2-7. Shows dynamic light scattering (DLS) data from the two polymers EPE(HD)-co-C8 and EPE(HD)-co-TG comparing the NPs in water to 4 days in (a) 1M NaOH; (b) 3M H₂O₂; and (c) 1M NaCl.

Whilst possible degradation in the presence of H₂O₂ was encouraging, the inability to observe any difference through a standard hydrolytic mechanism even after weeks was troubling and indicated

the system was too hydrophobic to degrade on a useful time frame. This marked an area of the design in need of alteration, something the latter half of the chapter will explore. All that said, these experiments were still conducted at room temperature and without the presence of natural catalysts such as esterases that might accelerate the process. As such, experiments are currently underway that employ the following design. In brief, an aliquot of the sample would be dried in the lid of an Eppendorf tube, to this would be added water/buffer, in some cases containing esterase, and a dialysis membrane pinned in place by attaching the rest of the tube (**Figure 2-8**). This experiment will allow more meaningful analysis of degradation by inspection of the supernatant in the main body of the tube through UV-vis spectroscopy whilst GPC, matrix assisted laser desorption/ionization time of flight (MALDI-ToF) mass spectroscopy and mass changes can be used to assay the material remaining in the lid.

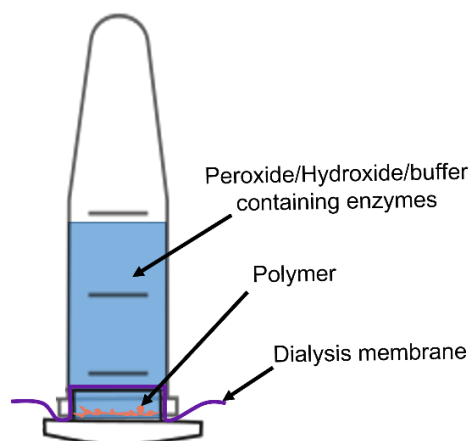


Figure 2-8. Schematic showing the set up currently employed for a more complete analysis of any possible degradation

2.3.1.5 - Design issues

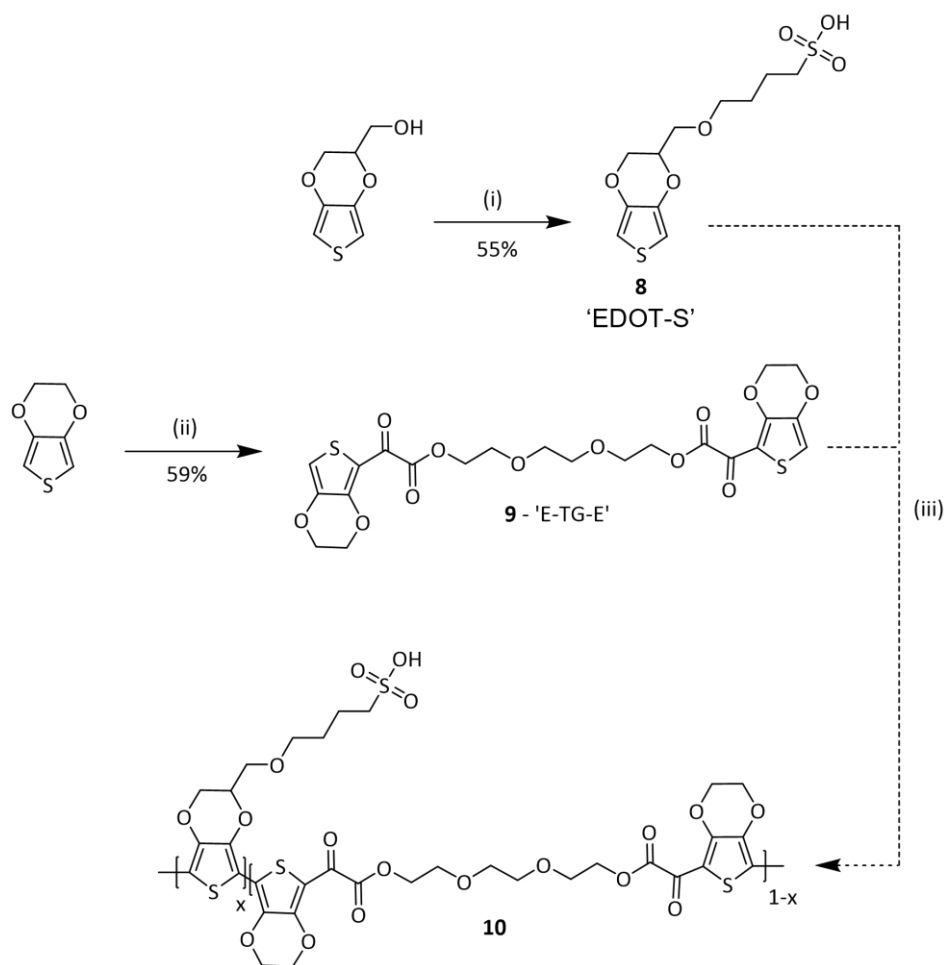
Although promising, these designs fall short in a few crucial areas. Firstly, polymer hydrophobicity limits processability and, as mentioned, likely restrains the rate of degradation to just surface erosion. Second, an external dopant is required to act as the counter ion in the doping process. An ideal degradable polymer solution should covalently incorporate a dopant into its backbone chemistry to prevent, potentially toxic, dopant leaching and maintain sufficient charge transport properties. As such, subsequent designs were investigated that could include a covalently linked dopant.

2.3.2 - Design 2.0 – Oxidative polymerisation

As outlined in Chapter 1, self-doped, sulfonated PEDOT (PEDOT-S) has been successfully synthesised primarily through oxidative polymerisation methods. Iron or ammonium-based oxidants are commonly used, often with catalytic amounts of $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$, and polymerisations can be run at room temperature in aqueous solvent systems.^{137–139}

It was reasoned that incorporating a degradable linker into a standard oxidative polymerisation with a self-doped EDOT co-monomer would yield the ideal conductive, degradable polymer. An obvious linker would utilise the chemistry of Spicer et al.¹⁹⁴ to cap both ends of a diol such as triethylene glycol (9 of **Scheme 2-2**). **Scheme 2-2**. Synthetic pathway attempted for oxidative polymerisation of a degradable PEDOT derivative. Conditions: (i) NaH, 1,4-butanedisulfone, toluene, 4 hours, 110 °C; (ii) oxalyl chloride, triethylene glycol at 100 °C for 1 hour, triethylamine, dioxane at room temperature for 3 hours; (iii) ammonium persulfate, iron sulfate, aqueous sulfuric acid, room temperature for 18 hours. Note 10 is a statistical mix with an average of 4 units EDOT-S to 1 unit E-TG-E., hereon denoted as E-TG-E). Pleasingly, with the correct stoichiometry and dropwise addition of TEG, E-TG-E was readily synthesised. Application of 1 M NaOH was then shown by NMR to degrade this monomer to its TEG and EDOT-acid constituents, confirming possible utility as a linker degradable by hydrolysis (Appendix II - **Figure A 1**). To form the polymer, an EDOT-sulfonate was synthesised (EDOT-S – 8 of **Scheme 2-2**) and copolymerisation attempted with E-TG-E.

Initial efforts adapted the protocol recently published by Yano et al.¹³⁹, in which they utilised an ammonium persulfate oxidant and an iron sulphate catalyst, with a 1:1 ratio of THF:1 M H_2SO_4 (aq.) required to dissolve the organic soluble E-TG-E linker. Encouragingly, a dark solution was found after ~18 hours indicating successful polymerisation. DMF gel permeation chromatography (GPC) traces confirmed polymeric species were present with molecular weights of > 10 kDa. Purification was undertaken using de-salting columns, but subsequent NMR analysis could not give conclusive evidence as to E-TG-E incorporation. Pleasingly however the polymer showed excellent water solubility as expected. Unfortunately, following stirring in 1 M NaOH and additional de-salting, the polymer peak in GPC, although slightly decreased in intensity possibly from the de-salting after hydroxide stirring, changed neither shape nor position, indicating no degradation and a lack of E-TG-E inclusion into the polymer backbone.



Scheme 2-2. Synthetic pathway attempted for oxidative polymerisation of a degradable PEDOT derivative. Conditions: (i) NaH, 1,4-butanedisulfone, toluene, 4 hours, 110 °C; (ii) oxalyl chloride, triethylene glycol at 100 °C for 1 hour, triethylamine, dioxane at room temperature for 3 hours; (iii) ammonium persulfate, iron sulfate, aqueous sulfuric acid, room temperature for 18 hours. Note 10 is a statistical mix with an average of 4 units EDOT-S to 1 unit E-TG-E.

Lack of degradation implied the degradable linker might not have been installed. It was reasoned that a possible cause was lack of solubility in the solvent system of either the E-TG-E or any E-TG-E-based oligomers that form. A range of conditions were therefore investigated as shown in **Table 2-1** below. Unfortunately, none investigated were able to provide a polymer capable of degradation by GPC despite E-TG-E being clearly soluble.

Table 2-1. Various conditions attempted to fully solubilise E-TG-E in an oxidative polymerisation

Solvent	Temperature (°C)
DMF	25
DMF/1M H ₂ SO ₄ (aq)	25
DMF/1M H ₂ SO ₄ (aq)	50
THF/1M H ₂ SO ₄ (aq)	50

Considering this, and given the easy cleavage of the degradable linker previously mentioned, it was then hypothesised that E-TG-E was not incorporated due to a mismatch in oxidation potentials preferentially polymerising just EDOT-S. This seemed reasonable given the possible stabilising effect, both inductively and through resonance, of oxalyl capping to the thiophene moiety. To further support this rationale, density functional theory calculations were performed on the two monomers to gain an estimate of the first ionisation energy and thus which might be polymerising preferentially. It was found that the energy of the highest occupied molecular orbital (HOMO) were -5.87 eV and -6.27 eV for EDOT-S and E-TG-E respectively. The deepened HOMO of E-TG-E is likely due to some resonance into the oxalyl group (see **Figure 2-9**) causing greater stability. Oxidation of E-TG-E is therefore less likely and as such so is its incorporation into the forming polymer chain. Note only half E-TG-E was modelled to save on computing since it was assumed both EDOT moieties would show the same ionisation potential.

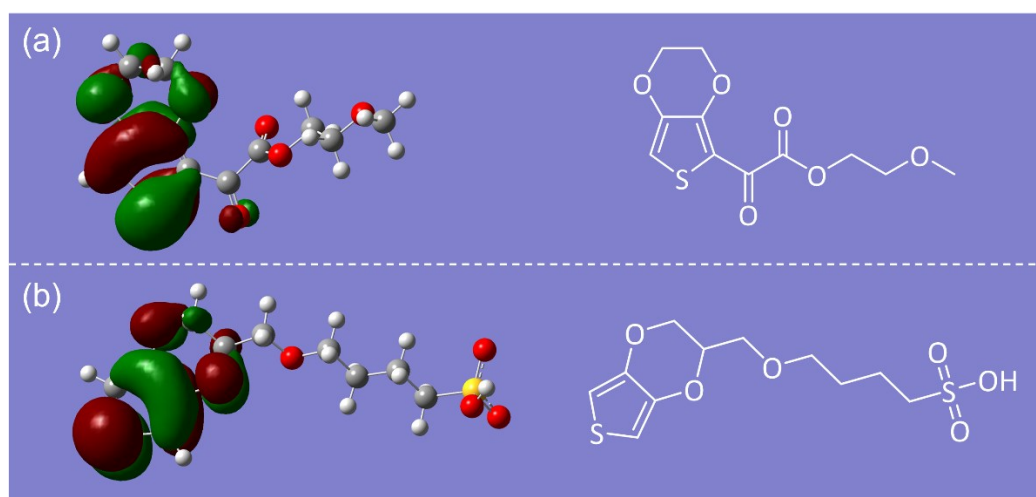


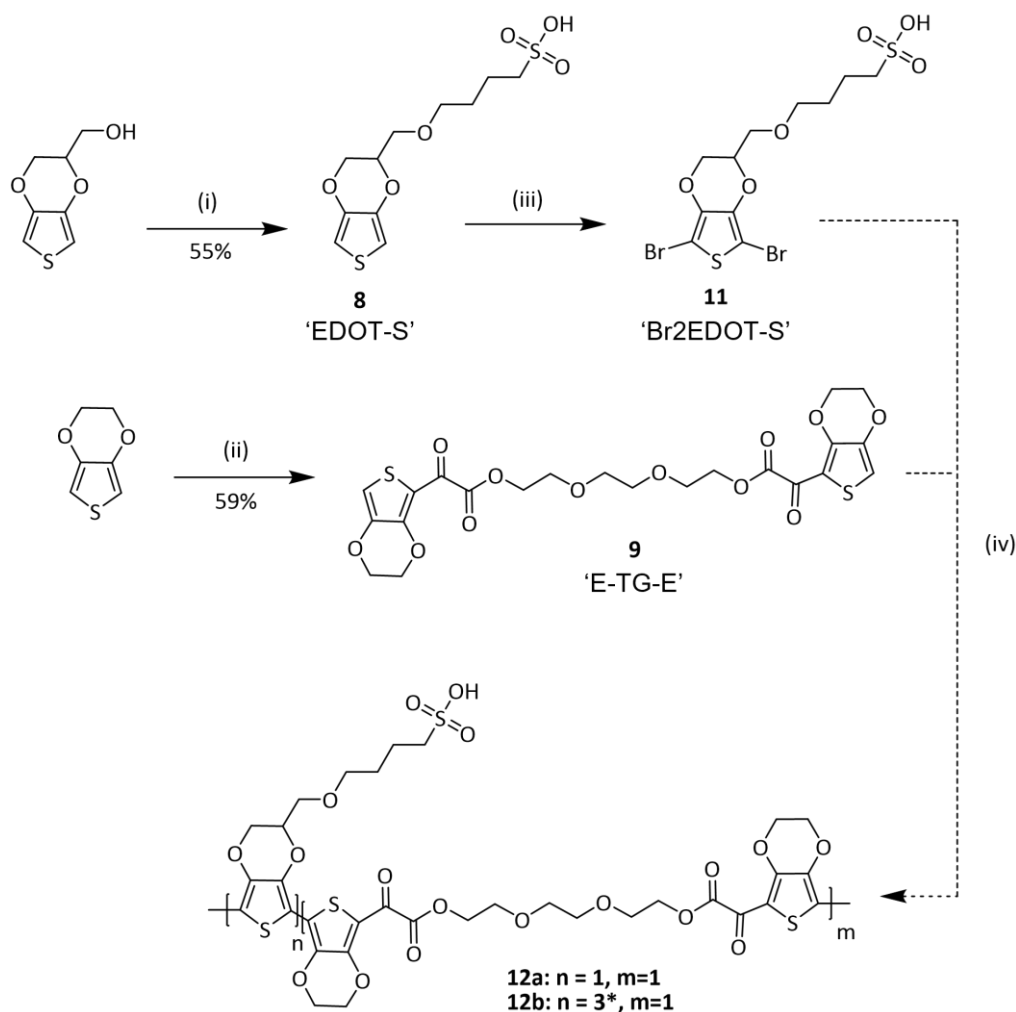
Figure 2-9. Visualisation of the surfaces calculated by DFT for (a) an approximation of E-TG-E where only half the molecule is modelled (since both ends were assumed to be identical with regards to oxidation potential) and (b) EDOT-S. Inspection of (a) reveals some electron density in the first carbonyl that may contribute to its greater stability and deeper HOMO level.

Given a self-doped polymer incorporating the degradable E-TG-E linker could not be achieved through an oxidative mechanism, another avenue less sensitive to relative oxidation potentials was required. On an interesting side note, during synthesis of **8** it was found that the presence of even trace amounts of aqueous acid (0.1 vol. %) would cause polymerisation of the monomer if left in ambient conditions for more than a day. Were time permitting, it would be enlightening to investigate such a phenomenon since it speaks to the nature and implications of acid doping, as well as its relationship to oxidative polymerisation mechanisms.

2.3.3 - Design 2.0 – Direct (hetero)arylation polymerisation

Considering the issues experienced with relative oxidation potentials for polymerisation, an alternative method was investigated in parallel. It was reasoned that a synthetic design that utilised the well-established direct (hetero)arylation polymerisation (DHAP) outlined in the previous chapter might provide an efficient solution since such chemistry should be independent of oxidation energies and enforce an ABAB structure. As shown in **Scheme 2-3** below, this was attempted by simply brominating **8** to give **11** followed by standard DHAP conditions in the presence of E-TG-E. Inclusion of **8** as well could allow for systems with extended conjugation from 3 to, on average, 5 repeat units if a 1:1:2 ratio of E-TG-E:Br₂EDOT-S:EDOT-S were used.

It should be noted that the polymerisation could equally be achieved through bromination of **9** and copolymerisation with **8**. Curiously, however standard NBS protocols were unable to produce the dibrominated product of E-TG-E, mono-substituted or otherwise. Since it was known from experience that EDOT capped with triethylene glycol monomethyl ether (TEGME) could readily be brominated, and this should be electronically identical at the sight of bromination, it was thought an intra/inter molecular complex formation was occurring that might restrict access of the Br₂ in the NBS mechanism. Higher temperatures will be investigated to navigate this issue should the product prove essential. Bromination of EDOT-S for **11** is thought to have been successful based upon NMR spectroscopy and LCMS analysis however purification is ongoing since, despite multiple routes, impurities are persistently seen by ¹H NMR spectroscopy. Nonetheless given the literature precedent, it is hoped the final polymerisation in the following step will be facile.^{140,194}



Scheme 2-3. Synthetic scheme to be employed for synthesis of a degradable PEDOT derivative through direct (hetero)arylation polymerisation. Conditions: (i) NaH, 1,4-butanedisulfonic acid, toluene, 4 hours at 110 °C; (ii) oxalyl chloride, triethylene glycol at 100 °C for 1 hour, triethylamine, dioxane at room temperature for 3 hours; (iii) N-bromosuccinimide, DMF at room temperature for 18 hours; (iv) $\text{Pd}(\text{OAc})_2$, PivOH, K_2CO_3 , **8** for **12b**, 140 °C for 18 hours. *Note **12b** would be a statistical mix with an average of $n=3$.

2.4 - Conclusions and future work

In conclusion, several designs for a degradable, conductive PEDOT have been explored. In the first design, a trimeric EDOT oligomer was copolymerised using basic polyesterification techniques to afford oligo-EDOT-based polyesters of high molecular weight. These materials were thoroughly characterised for their optoelectronic, conductive and degradation properties. It was found they showed energy gaps not dissimilar to PEDOT with data indicating conductivities in the 10^{-2} - 10^{-4} S/cm range. Degradation experiments so far have suggested the more hydrophilic of the two, EPE(HD)-co-TG, is susceptible to degradation when exposed to hydrogen peroxide, a reactive oxygen species found

in metabolic pathways of the body. It was found, however, that the polymers in this first design were potentially too hydrophobic. This would limit their rate of degradation and could make them difficult to combine with other biopolymers to, for instance, create useful scaffolds or hydrogel systems. Furthermore, this first design would likely require an external dopant to maintain charge transport performance which can leach out and be potentially toxic.

In light of this, a second design was presented that incorporated a sulfonate tethered to the polymer backbone. It was found that employing oxidative polymerisation conditions was unable to copolymerise the system however likely owing to a difference in oxidation potential of the comonomers. As such the synthesis was altered to incorporate direct(hetero)arylation polymerisation (DHAP) in the hope this would circumnavigate the issue. Encouragingly a test reaction using a brominated **2a** and the degradable linker (**9**) showed molecular weights of 8-10 kDa by MALDI-ToF demonstrating E-TG-Es ability to participate in DHAP.

This synthesis is currently in progress and if successful the material will be fully characterised as in the first design including the more rigorous degradation studies to properly elucidate the process. It is hoped this more water soluble system being chemically mimetic of PEDOT:PSS will allow it to be processed using some of the innovative techniques developed for this ubiquitous polymer including porous scaffold and hydrogel formation. Ultimately it is anticipated that such a degradable derivative of PEDOT:PSS will find utility in a range of applications both in bioengineering and beyond where impermanent electronics might be desired.

2.5 - Experimental

All details not included here regarding material and characterisation can be found in the general experimental section of Appendix II. NMRs can be found in Appendix III.

2.5.1 - Characterisation

2.5.1.1 - High Performance Liquid Chromatography (HPLC) Purification

For EDOT-S, HPLC purification was performed on a Shimadzu FRC-10A with a typical flow rate of 10 ml/min. In a typical purification the molecule (50 – 100 mg) was dissolved in H₂O/MeCN by first adding 20 mL H₂O and then slowly adding up to 20 mL of MeCN until dissolved. This required dissolution in

0-5% MeCN in water. This was then filtered through a 0.45 μ m Teflon filter and applied to the column with a starting H₂O/MeCN concentration to match that in which dissolution occurred. Typically, the H₂O/MeCN gradient would be as follows: Isocratic at 5% MeCN for 10 minutes, increase to 50% over 10 minutes, hold at 50% for 5 minutes, return to 5% for 5 minutes. Collected fractions would be dried of MeCN on a rotary evaporator then freeze dried to yield the final product with high purity.

2.5.1.2 - Degradation studies

Degradation experiments evolved as the research progressed

Design 1.0

In solid – To a pre-weighed vial was added the polymer (~ 1 mg) in chloroform (500 μ l) and allowed to evaporate to dryness. To the residue was then added 1 mL of 1M NaOH and the vial left for 2 weeks at room temperature. After this the water was dried off under gentle nitrogen blowing, the sample dissolved in DMF containing 0.05 % LiBr (usually taken directly from the GPC stock), filtered through a 0.45 μ m Teflon filter and submitted for GPC. Weights were initially planned to be taken after nitrogen blowing but it was reasoned the weight change would be too small, which would introduce too great an error when combined with delamination issues discussed in the main text this would severely limit the utility of any results.

In solution – The requisite polymer (~ 1 mg) was dissolved in DMF (500 μ l) following which either 500 μ l of 1M NaOH or 3M H₂O₂ was added and the mixture stirred overnight. Following this the sample was dried under nitrogen, redissolved in DMF containing 0.05 % LiBr and run on the GPC.

Through dialysis membrane – To the pre-weighed lid of an Eppendorf was added the polymer in THF (~200 μ l) and allowed to evaporate to dryness. To this was added either 200 μ l of 1M NaOH or 200 μ l of 2.5 mg/mL of pig liver lipase and the rest of the Eppendorf added to seal in a dialysis membrane (**Figure 2-8**) with 5-7 kDa cutoff. These tubes were to be agitated gently at 37 °C for 3 weeks.

Through nanoparticles – Nanoparticles were formed by nanoprecipitation: A 3 mg/mL solution in THF was prepared and filtered through a 0.2 μ m Teflon filter. 100 μ l of this was then injected into 1 mL of deionised water and pumped repeatedly with the syringe. The THF was evaporated off through nitrogen bubbling then filtered through a 0.2 μ m Teflon filter. To this was then added either 1M NaOH, 3M H₂O₂ or 1M NaCl to give 1:1 equivalents. DLS data was collected on a Malvern Zetasizer providing data on the intensity, number and volume size distributions. As discussed in the main text, data was

collected after nanoparticle formation and after incubation at room temperature for 4 days with the reagents mentioned above.

Design 2.0

For a proof of concept experiment the following protocol was undertaken. In a typical experiment the polymer was suspended in a THF:Water mixture (~10 ml) containing 3-4 mL of 1M NaOH at room temperature. This was allowed to stir overnight after which point the mixture was dried of THF by nitrogen bubbling, lyophilised, passed through a size exclusion column to de-salt, lyophilised again, dissolved in DMF, filtered through a 0.2 μ m PTFE filter and submitted for GPC.

2.5.1.3 - Thin film formation

Thin films were formed primarily through spin coating. Different polymers required different conditions but the most common conditions are stated here. Substrates were cut into squares of roughly 10 x 10 mm and cleaned through sonication in detergent, water, acetone and iPrOH followed by nitrogen drying. Typically, polymers would be suspended in THF optimally at 5 mg/mL and deposited on the films in around 10-20 μ l aliquots prior to spinning. Surprisingly it was commonly found the best films could be produced through spinning first at 4-500 rpm for 45s followed by 1500-2000 for 20s.

2.5.1.4 - Four-point probe conductivity measurements

Measurements were taken on an Ossila 4-point probe. Materials were prepared by immersion or spin coating on glass slides previously cleaned as detailed above. Film thickness was estimated using AFM and entered into the software for conductivity estimation. Inhomogeneity of the films created large uncertainty in the obtained values and will require more repeats.

2.5.1.5 - Cyclic voltammetry

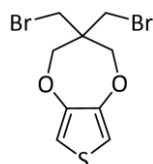
Data was collected in 0.1 M Tetrabutylammonium perchlorate (TBAP) in acetonitrile. A thin film was deposited using 5 μ L of a ~ 1 mg/mL solution on a glassy carbon electrode with a platinum counter electrode and Ag/Ag⁺ reference. At the conclusion of every experiment, ferrocene was added to the electrolyte and the CV trace of this collected to be subtracted from the working electrode data. To move from Ag/Ag⁺ to Fe/Fe⁺ the redox potential of ferrocene was calculated as halfway between the oxidation and reduction peaks. This was calculated as $0.547 + 0.5 \times (0.625 - 0.547) = 0.586$ V.

2.5.2 - Synthesis

General notes on materials and instruments can be found in Appendix I. NMR spectra and other supplementary characterisation data can be found in Appendix II and III, Chapter 3.

2.5.2.1 - Small molecules

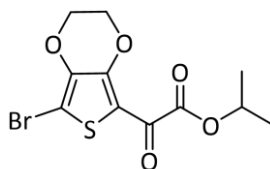
ProDOT-(CH₂Br)₂: 3,3-bis(bromomethyl)-3,4-dihydro-2H-thieno[3,4-b][1,4]dioxepine (**1**)



Compound was prepared according to the method of Ponder et al. with a yield of 73% and NMR spectroscopic data was found to be consistent with previous literature protocols.⁶⁵ ¹H NMR (400 MHz, CDCl₃): δ = 6.49 (2H, s), 4.10 (4H, s), 3.6 (4H, s).

ProDOT(HD): 3,3-bis(((2-hexyldecyl)oxy)methyl)-3,4-dihydro-2H-thieno[3,4-b][1,4]dioxepine (**2a**)

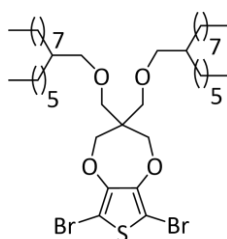
BrEDOT-OiPr: Isopropyl 2-(7-bromo-2,3-dihydrothieno[3,4-b][1,4]dioxin-5-yl)-2-oxoacetate (**4**)



Compound was prepared according to and NMR spectroscopic data was consistent with previous literature in a yield of 72%.¹⁹⁴ ¹H NMR (400 MHz, CDCl₃): δ = 5.17 (1H, h, J = 6.3 Hz), 4.36-4.33 (2H, m), 4.31-4.29 (2H, m), 1.33 (6H, d, J = 6.3 Hz) ppm.

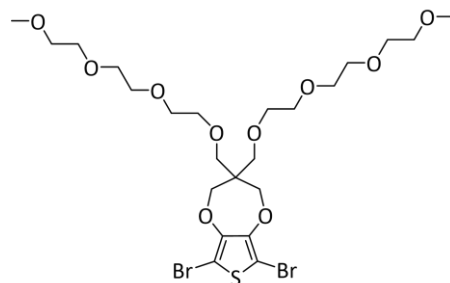
Although not included in the main text, initially trimers were constructed around a dibromo-ProDOT derivative rather than brominating EDOT-OiPr (**3**). The following two compounds are therefore detailed.

Br2-ProDOT(HD): 6,8-dibromo-3,3-bis(((2-hexyldecyl)oxy)methyl)-3,4-dihydro-2H-thieno[3,4-b][1,4]dioxepine



Compound was prepared according to and NMR spectroscopic data was consistent with previous literature in a yield of 62%.⁶⁵ ¹H NMR (400 MHz, CDCl₃): δ = 4.08 (4H, s), 3.47 (4H, s), 3.26 (4H, d, J = 5.7 Hz), 1.52 (2H, p, J = 5.6 Hz), 1.33-1.21 (48H, m), 0.92-0.85 (12H, m)

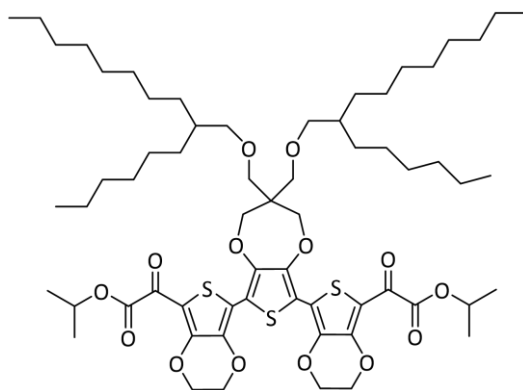
Br2ProDOT(TG): 6,8-dibromo-3,3-di(2,5,8,11-tetraoxadodecyl)-3,4-dihydro-2H-thieno[3,4-b][1,4]dioxepine



The protocol was adapted from previously seen in the literature.⁶⁵ To a 100 mL RBF was added the ProDOT(TG) and charged under nitrogen with a balloon. Separately, CHCl₃ was degassed using a nitrogen balloon for ~20 minutes. The Chloroform (20 mL) was then transferred to the reaction flask followed by the NBS. The mixture was stirred in the dark with a nitrogen balloon overnight. The reaction was monitored by TLC and when complete was dry loaded directly onto silica. The mixture was purified by column chromatography using a 50-100% gradient of EtOAc in DCM giving the desired product in a yield of 30%. ¹H NMR (400 MHz, CDCl₃): δ = 4.07 (4H, s, -C-O-CH₂), 3.63-3.56 (20H, m, ethylene glycol protons), 3.54 (4H, s, -C-CH₂-O-), 3.53-3.50 (4H, m, CH₂-OMe), 3.35 (6H, s, -O-CH₃). ¹³C NMR (75 MHz, CDCl₃): δ = 147.14, 145.06, 91.22, 74.18, 72.02, 71.16, 70.69, 70.42, 69.96, 59.10, 48.01, 30.01 ppm. LRMS *m/z* ESI+: Calc: 666.05 Found: 666.9 [M+H]⁺, 684.0 [M+NH₄]⁺.

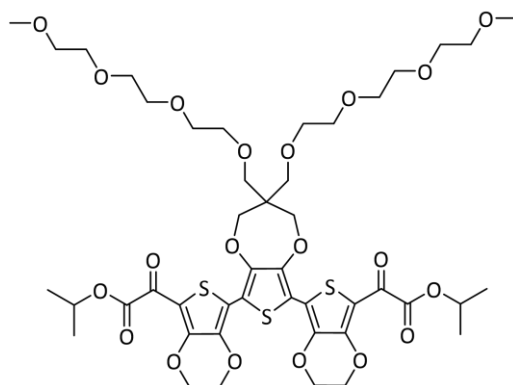
General procedure for EPE-OiPr small molecules: In general, to a microwave vial was added the requisite ProDOT derivative (1 eq. – typically 100 mg scale), BrEDOT-OiPr (2.3 eq.), Pd(OAc)₂ (0.05 eq.), pivalic acid (0.5 eq.) and potassium carbonate (5 eq.). A stirring bar was fitted and the vial sealed under nitrogen following which DMF (5 mL) was added and mixture stirred at 90 °C for 2 hours. The reaction was then cooled to room temperature whereupon most DMF was evaporated off under nitrogen. DCM (200 mL) was added and the mixture washed twice with water (2 x 50 mL), once with brine (50 mL), the organic layer dried with MgSO₄, filtered and concentrated for column chromatography.

EPE(HD)-OiPr₂: Diisopropyl 2,2'-((3,3-bis(((2-hexyldecyl)oxy)methyl)-3,4-dihydro-2H-thieno[3,4-b][1,4]dioxepine-6,8-diyl)bis(2,3-dihydrothieno[3,4-b][1,4]dioxine-7,5-diyl))bis(2-oxoacetate) (**5a**)



Purified using 20-50% EtOAc in hexanes with a yield of 79%. ^1H NMR (400 MHz, CDCl_3): δ = 5.23 (2H, h, J = 6.3 Hz, $\text{CH}-(\text{CH}_3)_2$), 4.43-4.37 (8H, m, $\text{CH}_2-\text{O}-$), 4.25 (4H, s, $\text{C}-\text{CH}_2-\text{O}-$), 3.57 ($\text{C}-\text{CH}_2-\text{O}-\text{CH}_2$), 3.29 (4H, d, J = 5.7 Hz, $-\text{O}-\text{CH}_2$ (hexyldecyl alkyl protons)), 1.57-1.52 (2H, m, $\text{O}-\text{CH}-(\text{CH}_3)_2$), 1.37 (12H, d, J = 6.2 Hz, $\text{CH}_3(\text{O}^i\text{Pr})$), 1.31-1.19 (56H, m, Hexyldecyl- CH_2) 0.88-0.82 (12H, m, hexyldecyl- CH_3); ^{13}C NMR (400 MHz, $\text{DMSO}-d_6$): δ = 176.26, 163.51, 147.58, 147.42, 137.04, 123.07, 114.98, 112.12, 76.81, 70.34, 70.23, 65.34, 64.69, 32.09, 31.60, 30.15, 29.80, 29.38, 26.94, 22.71, 21.93, 21.82, 14.09 ppm. Awaiting mass spectroscopy data.

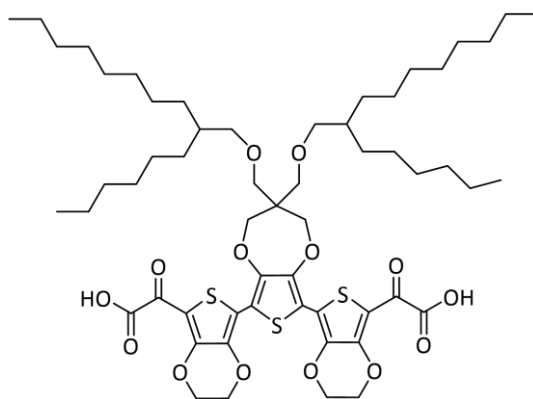
EPE(TG)-OiPr₂: Diisopropyl 2,2'-((3,3-di(2,5,8,11-tetraoxadodecyl)-3,4-dihydro-2H-thieno[3,4-b][1,4]dioxepine-6,8-diyl)bis(2,3-dihydrothieno[3,4-b][1,4]dioxine-7,5-diyl))bis(2-oxoacetate) (**5b**)



A clean NMR could not be obtained for this compound however as detailed in the main text the subsequent di-acid was synthesised directly through accidental ester cleavage at high direct arylation coupling temperatures.

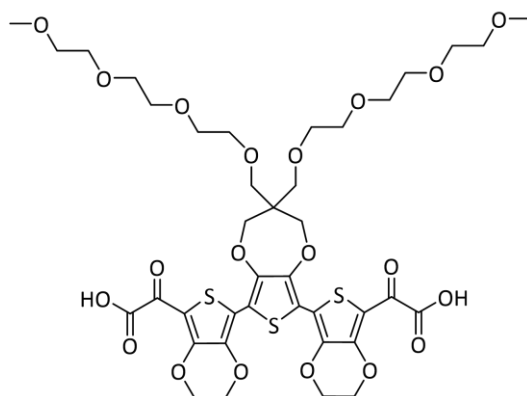
General procedure for EPE-COOH2: In general the requisite EPE-OiPr small molecule was dissolved in THF and an excess (>5 eq.) of 1M NaOH (aq.) added. The mixture was left to stir for at least 2 hours following which it was acidified using 1M HCl (aq.), centrifuged, the supernatant replaced with water and centrifuged again, this final step would typically be repeated 2 times. The resulting solid was dried either under nitrogen or by lyophilisation.

EPE(HD)-COOH2: 2,2'-((3,3-bis(((2-hexyldecyl)oxy)methyl)-3,4-dihydro-2H-thieno[3,4-b][1,4]dioxepine-6,8-diyl)bis(2,3-dihydrothieno[3,4-b][1,4]dioxine-7,5-diyl))bis(2-oxoacetic acid) (**6a**)



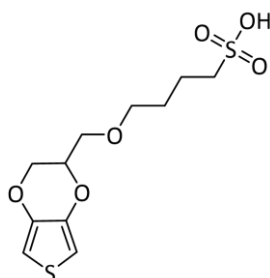
NMR spectroscopy was unfortunately broad due to a low solubility. Efforts are ongoing to obtain mass spectroscopy data, however although broad the NMR was as expected for the desired product and at this point was tentatively assumed pure with giving a quantitative yield of 99%. ^1H NMR (400 MHz, DMSO- d_6): δ = 4.47 (8H, br, EDOT-dioxy protons), 4.19 (4H, br, -C-O-CH $_2$), 3.49 (4H, br, C-CH $_2$ -O-alkyl), 1.23 (48H, br, alkyl protons), 0.81 (12H, t, alkyl-CH $_3$). ^{13}C NMR (75 MHz, DMSO- d_6): δ = 166.15, 147.55, 120.80, 115.07, 111.53, 74.53, 69.43, 48.23, 38.00, 31.85, 31.57, 29.99, 29.68, 29.53, 29.25, 26.74, 22.63, 14.42.

EPE(TG)-COOH2: 2,2'-((3,3-di(2,5,8,11-tetraoxadodecyl)-3,4-dihydro-2H-thieno[3,4-b][1,4]dioxepine-6,8-diyl)bis(2,3-dihydrothieno[3,4-b][1,4]dioxine-7,5-diyl))bis(2-oxoacetic acid) (**6b**)



Purified on HPLC using 5-50% MeCN in water with 0.1% NH_4OH giving a yield of 3 %. ^1H NMR (400 MHz, DMSO-d_6): δ = 4.33 (4H, m, EDOT-dioxy ring protons), 4.27 (4H, m, EDOT-dioxy ring protons), 4.10 (4H, s, C-O-CH₂ on ProDOT dioxy ring), 3.57 (4H, s, CH₂-C-CH₂), 3.50 (24H, m, ethylene glycol protons), 3.37 (6H, m, O-CH₃). Insufficient material was produced to obtain a carbon NMR of the product. Reaction suspected a success but insufficient data was present at this point to be conclusive, investigations are ongoing.

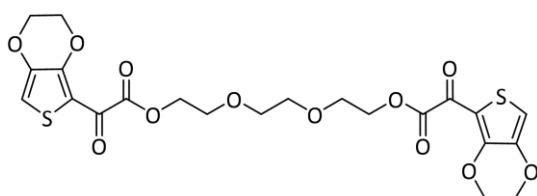
EDOT-S: 4-((2,3-dihydrothieno[3,4-b][1,4]dioxin-2-yl)methoxy)butane-1-sulfonic acid (**8**)



Protocol was adapted from and NMR found to be consistent with that previously reported.¹⁴⁰ In brief a microwave vial of NaH (60% in mineral oil) (57 mg, 1.15 eq.) and EDOT-Me-OH (200 mg, 1 eq.) was charged under nitrogen and to this was added 5 mL Toluene. This was bubbled with nitrogen to remove any excess oxygen for around 20 minutes following which the reaction was heated to reflux for 2 hours. After cooling to room temperature, the 1,4-butane sultone (169 mg, 1 eq.) was added and the reaction again refluxed for 2 hours. After this the mixture was cooled to room temperature and dried under nitrogen overnight. The resulting solid was washed out with acetone into a Corning vial and centrifuged/washed 2x with acetone. This was then dissolved in a solution of 5% MeCN in water

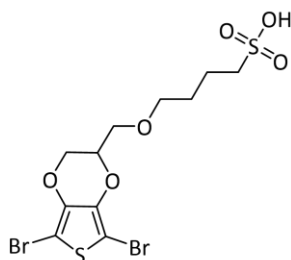
(all HPLC grade) with 0.1% NH₄OH added and run in basic conditions (0.1 % NH₄OH) on the HPLC using a 5-50% MeCN gradient. Fractions were lyophilised and the desired product obtained as a white powder in a yield of 55%. NMR consistent with that previously reported.¹⁴⁰ ¹H NMR (400 MHz, CDCl₃): δ = 6.53z (2H, s), 4.45-4.40 (1H, m), 4.17 (1H, dd, *J* = 12.0, 2.2 Hz), 4.10 (1H, dd, *J* = 12.0, 7.0 Hz), 3.80-3.70 (2H, m), 3.65-3.58 (2H, m), 3.01-2.88 (2H, m), 1.87-1.65 (4H, m) ppm.

E-TG-E: (ethane-1,2-diylbis(oxy))bis(ethane-2,1-diyl) bis(2-(2,3-dihydrothieno[3,4-b][1,4]dioxin-5-yl)-2-oxoacetate) (**9**)



To a 250 mL RBF was added EDOT and dioxane (~20 ml). This was allowed to stir following which the Oxalyl Chloride was slowly added drop-wise. This was heated to 100C for 1 hour at which point the mixture was allowed to cool to room temperature and the TEG (dissolved in ~10 mL Dioxane) and Et₃N was added slowly, drop-wise at the same time. This was allowed to stir for a further 2 hours whilst being monitored by TLC. The reaction mixture was diluted with DCM, washed once with water, once with brine, dried over MgSO₄, filtered and concentrated on the rota vap onto silica for dry loading on an automated flash column with a 70-100% EtOAc in Hexanes gradient. This gave the desired product in a 59% yield as a thick brown oil. ¹H NMR (400 MHz, CDCl₃): δ = 6.80 (2H, s, -S-CH), 4.41-4.35 (4H, m, -COO-CH₂), 4.33-4.28 (4H, m, EDOT dioxy ring: -O-CH₂-CH₂-O-), 4.21-4.15 (4H, m, EDOT dioxy ring: -O-CH₂-CH₂-O-), 3.76-3.68 (4H, m, -COO-CH₂-CH₂), 3.60 (4H, s, -O-CH₂-CH₂-O-). ¹³C NMR (75 MHz, CDCl₃): δ = 163.07, 148.87, 141.87, 113.09, 70.85, 68.75, 65.69, 65.39, 64.11. LRMS *m/z* ESI+: Calc: 542.06, Found 543.0 [M+H]⁺, 560.0 [M+NH₄]⁺ and 564.9 [M+Na]⁺

Br2EDOT-S: 4-((5,7-dibromo-2,3-dihydrothieno[3,4-b][1,4]dioxin-2-yl)methoxy)butane-1-sulfonic acid (**11**)

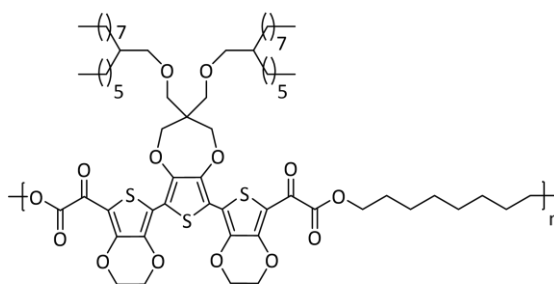


Protocol was adapted from and NMR found to be consistent with that previously reported.¹⁴⁰ In a 5 mL RBF was weighed the EDOT-S (105 mg, 1 eq.) and a stirring bar added, this was placed under nitrogen via a balloon. Separately, a stock of DMF (50 mL) was degassed with argon in a 100 mL RBF for 20-30 minutes. ~1mL of this was added to the EDOT-S to dissolve. This was wrapped in foil, placed in ice and the NBS (151 mg, 2.5 eq.) added quickly with a nitrogen balloon needle still in to preserve inert atmosphere. After stirring overnight the reaction mixture was precipitated into acetone (100 mL). From this point multiple purification methods have been/are being pursued with issues in achieving total purity currently persisting.

2.5.2.2 - Polymers

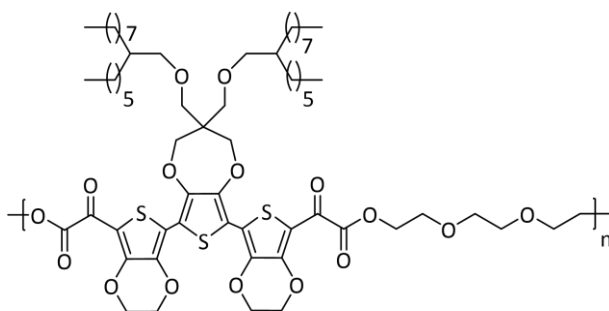
EPE polyester general protocol: To a 250 mL RBF was added the requisite EDOT trimer and co-monomer (triethylene glycol or 1,8-octanediol), toluene, and the setup fitted with a stirring bar and Soxhlet apparatus containing a cellulose thimble with 4 Å molecular sieves. The mixture was refluxed for up to 4 days, following which the toluene was removed under reduced pressure, the residue was then dissolved in THF and dialysed for a week using a 10 kDa cutoff membrane.

EPE(HD)-co-C8: Poly(2,2'-((3,3-di(2,5,8,11-tetraoxadodecyl)-3,4-dihydro-2H-thieno[3,4-b][1,4]dioxepine-6,8-diyl)bis(2,3-dihydrothieno[3,4-b][1,4]dioxine-7,5-diyl))bis(2-oxoacetic acid)-co-1,8-octanediol) (**7a**)



Yield of 82%. ^1H NMR (400 MHz, DMSO-d_6): δ = 1.26 (48H, br, hexyldecyl protons), 0.85 (12H, br, hexyldecyl terminal CH_3). All other protons could not be properly observed due to peak broadening and noise likely due to being on or close to the polymer backbone. M_w : 290 kDa, PD = 2.00 by GPC relative to a PMMA standard.

EPE(HD)-co-TG: Poly(2,2'-((3,3-di(2,5,8,11-tetraoxadodecyl)-3,4-dihydro-2H-thieno[3,4-b][1,4]dioxepine-6,8-diyl)bis(2,3-dihydrothieno[3,4-b][1,4]dioxine-7,5-diyl))bis(2-oxoacetic acid)-co-triethylene glycol) (**7b**)



Yield of 55%. ^1H NMR (400 MHz, DMSO-d_6): δ = 1.28 (48H, br, hexyldecyl protons), 0.90 (12H, br, hexyldecyl terminal CH_3). All other protons could not be properly observed due to peak broadening and noise likely due to being on or close to the polymer backbone. M_w : 142 kDa, PD = 1.49 by GPC relative to a PMMA standard.

Chapter 3 - Developing of functional Poly(3,4-ethylenedioxythiophene) derivatives for biomedical applications

3.1 - Introduction

So far in this thesis, the fabrication of fully degradable conducting polymer (CP) systems has been investigated. Whilst degradability is a long-standing challenge of conjugated polymer systems, other applications related to the biomedical sciences require derivatisation in different directions. As mentioned, the extensive potential of poly(3,4-ethylenedioxythiophene) (PEDOT) makes it the ideal substrate to add functionality to such that it might adapt to a range of innovative material properties and functions. In this chapter, the efforts made to derivatise EDOT/ProDOT monomers and polymers for applications, such as organic electrochemical transistor (OECT) and 3D printing, are detailed.

3.2 - Background

Material solutions to biomedical and tissue engineering challenges require systems acutely designed for interfacing biology through optimal mechanical, bio-functional, bio-compatible and morphological properties. In the domain of conductive biomaterials, particular consideration is required given the often rigid and hydrophobic nature of conjugated organic systems. As outlined in Chapter 1, poly(3,4-ethylenedioxythiophene) (PEDOT) has established itself as the polymer of choice when it comes to charge transporting applications in biomedicine and beyond, owing to its exceptional conductivity and stability.¹⁷ PEDOT alone, however, is brittle with no bio-functionality and highly insoluble; it requires a dopant polymer, commonly poly(styrene sulfonate) (PSS), to be processable at all. Accordingly, a plethora of derivatives have emerged, both for biomedical applications and beyond, that attempt to preserve the remarkable electronics of the polymer whilst revolutionising its solubility, functionality, processability and mechanical properties.

To focus first on monomer derivatisation, both 3,4-ethylenedioxythiophene (EDOT) and its cousin 3,4-propylenedioxythiophene (ProDOT), shown in **Figure 3-1a**, have been modified extensively. Easily accessible derivatives such as hydroxy-methyl-EDOT, chloro-methyl-EDOT, azido-methyl-EDOT and carboxy-methyl-EDOT allow for facile conjugation of a plethora of functional groups (**Figure 3-1b**).¹⁰⁴ These include alkyl,²⁰³ alkoxy,²⁰³ aryl,²⁰⁴ alkenyl,¹⁰⁴ alkynyl,²⁰⁵ thiol/amine/acrylate-terminated²⁰⁶ and acid-terminated²⁰⁷ to name a few.

A similar situation can be seen for ProDOT which is often appended with two moieties to each monomer on account of the commonly used di(bromo-methyl)-ProDOT (**1**) starting material (**Figure 3-1c**). Whilst the bulkier di-oxy ring of ProDOTs likely contributes to slightly lower conductivity from more chain twisting relative to EDOT, the former benefits from greater stability when brominated at the 2 and 5 positions of the thiophene ring. This makes ProDOT derivatives better candidates for the brominated species in direct arylation pathways with the presence of two functional groups furthering its appeal for many avenues, such as when increased solubility is desired.⁶⁵ Such chemical handles have been exploited to functionalise directly with bio-molecules. One example is the appending of laminin-derived peptides to a carboxy-functionalised PEDOT derivative via amide couplings. Here the authors demonstrated enhanced neurite outgrowth in rat pheochromocytoma (PC12) cells in the presence of the laminin peptide functionalised PEDOT and a poly(ethylene glycol) spacer.⁴¹

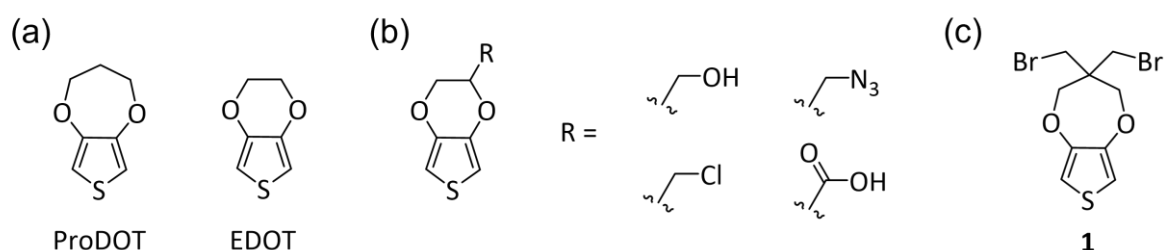


Figure 3-1. Figure depicting (a) the structure of EDOT and ProDOT; (b) common derivatives of EDOT most of which are commercially available; (c) a common starting point in ProDOT chemistry (**1** - already mentioned in Chapter 2) bearing two sites of electrophilicity.

Derivatisation during or post polymerisation has been investigated extensively through formation in the presence of a biomolecule that can simultaneously act as a stabiliser and a dopant.¹⁰⁴ These biomolecules have included dextran sulfate (DS),²⁰⁸ guar gum (GG),²⁰⁹ heparin (Hep),¹⁰⁴ hyaluronic acid (HA),¹⁰⁴ chondroitin sulfate (CS),²¹⁰ pectin,²¹¹ sulphated cellulose,²¹² glycosaminoglycans (GAGs) and even DNA.²¹³ Such architectures have then demonstrated improved bio-functionality such as

improved support of neuro-regeneration (HA, Hep and CS) or increased protection against cell death induced by peroxides (CS) relative to just PEDOT:PSS.²¹⁰ In some cases, minor improvements in conductivity of these materials are attractive options for bioelectrode, tissue engineering, biosensing and drug delivery applications. Indeed such systems have already demonstrated their utility with PEDOT:xanthan gum used to create porous scaffolds for tissue engineering,²¹⁴ PEDOT:GAGs for recording/stimulating neural activity,²⁰⁹ PEDOT:GG as longels²⁰⁹ and PEDOT:DS as a material for inkjet printing.²⁰⁸

With 3D printing technologies being able to create ever smaller and more intricate structures, PEDOT derivatives that might be used in such processes are of particular interest. To date a range of examples exist demonstrating ink-jet printing from PEDOT:PSS dispersions mixed with additives such as poly(ethylene glycol) or dimethylsulfoxide (DMSO).²¹⁵ The most advanced of these showed 3D printing behaviour with feature sizes down to 30 μm .²¹⁶ Printability can also be achieved through growing/grafting of appropriate polymers from the backbone of a PEDOT derivative. In work by Dominguez-Alfaro, racemic poly(lactic acid) (PLA) was polymerised off an EDOT monomer, which was subsequently made to form PEDOT oxidatively. This was shown to be printable through direct ink writing down to a feature size of 200 μm .²¹⁷

Though a range of innovative derivatives exist in the literature, there is still extensive scope for further explorations in this space. This chapter will therefore present a series of short stories around the EDOT/ProDOT derivatisation chemistry investigated throughout the PhD, first as small molecules and later as polymers designed for OECT or 3D printable applications.

3.3 - Results and Discussion

3.3.1 - Monomer derivatisation

Here a selection of synthetic avenues relating to the derivatisation of EDOT/ProDOT monomers will be discussed. The challenges faced will be outlined and the changes these lead to in the given synthetic approach. The first of these will examine derivatising EDOT with an aryl sulfonate moiety.

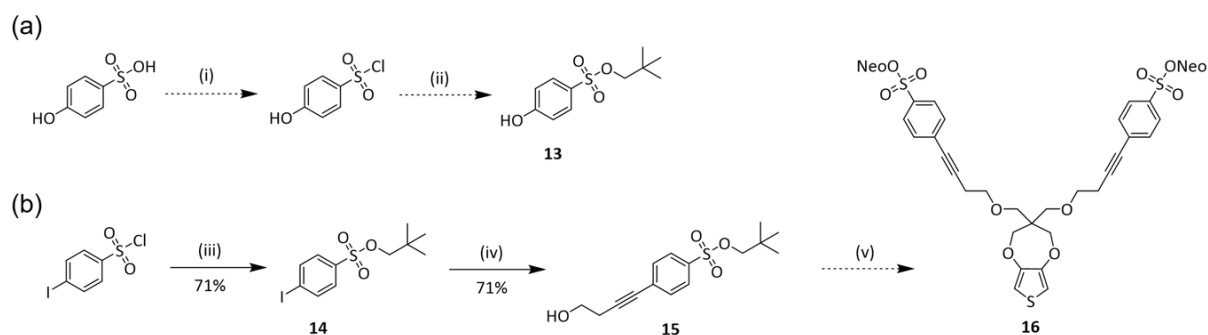
3.3.1.1 - Self-doping ProDOT with aryl sulfonate

Understanding of the phenomena of doping, whilst receiving increasing attention in recent years, still contains many unanswered questions. An example of an area still contested is the impact of counter anion identity on the resulting electronic properties, particularly conductivity. Whilst some authors have reported the relative insensitivity of charge transport to this parameter (e.g. negligible difference between Cl^- and toluenesulfonate $^-$ (Tos^-)),²¹⁸ others have found differences spanning orders of magnitude (e.g. between Poly(styrene sulfonate) (PSS^-), Tos^- and ClO_4^-)⁷⁵ with some even observing transformations from a semiconductor to a semi-metal.²¹⁹ That said, a common observation in maximising charge transport is the formation of crystalline PEDOT domains that can lower the barriers to inter-chain polaron movement. As such it has been predicted that counter-ions capable of intercalating with (semi)crystalline PEDOT domains might cause minimal disruption and help to maximise the conductivity of the system.²²⁰ For these reasons we felt it worthwhile to attempt self-doping not just with alkyl-sulfonate based counter-ion groups, as has been previously demonstrated,¹³⁹ but ideally with aryl-sulfonates. It was hoped that such a design would maximise any potential pi-pi stacking interactions and provide the electronic properties seen from the most common aromatic dopants PSS^- and Tos^- .

It was felt that use of the $\text{ProDOT}(\text{CH}_2\text{Br})_2$, **1**, electrophile would be the most prudent starting point for sulfonate conjugation. This therefore necessitated the synthesis of an appropriate nucleophilic aryl-sulfonate derivative. Initial attempts involved the use of a 4-hydroxybenzenesulfonic acid (**Scheme 3-1a**) where it was envisaged that following protection of the sulfonic acid, the hydroxyl group might be deprotonated for conjugation to the ProDOT electrophile (expected pK_a in the range of 8-10).²²¹ Unfortunately, the use of thionyl chloride to create a sulfonyl chloride for protection with trifluoroethanol (or similar) was unsuccessful likely due to interference with thionyl chloride from the unprotected phenol moiety that can react with oxidising and electrophilic reagents. Rather than

pursuing this route further through protecting steps, it was decided that the phenol hydroxy group may struggle to act as a decent nucleophile when deprotonated given resonance into the aromatic ring and as such alternative pathways were explored.

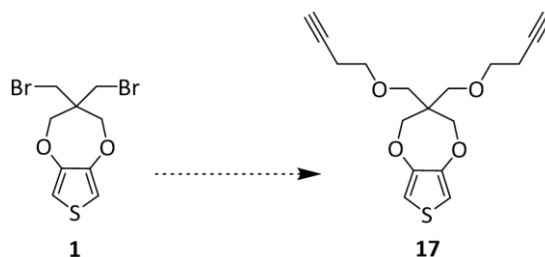
Fortuitously, a synthetic pathway to protected aromatic sulfonate conjugation was simultaneously being explored by others in the lab whereby 4-iodobenzylsulfonyl chlorides were protected and coupled to oligo-alkynes via Sonogashira chemistry.²²² With a slight change in the synthetic approach it was hoped this could be employed to solve the current challenge as shown in **Scheme 3-1b** below. Given potential uses in the degradable polymer work at the time (see chapter 2), a neopentyl protecting group was chosen owing to its stability in hydroxide as a result of steric crowding from the *tert*-Butyl group.²²³ Happily, sulfonic ester formation (**14** – 71% yield) and Sonogashira coupling to 3-butyn-1-ol proceeded without issue to give **15** with 71% yield at which point endeavours were made toward ProDOT conjugation. Unfortunately, when attempted in the presence of sodium hydride, a combination of degraded and deprotected products were observed but without trace of a mono- or di-substituted species by NMR. Although no data could be found in the literature as to hydride deprotections of sulfonates, given the suggestion of cleaved neopentyl alcohol, it was possible traces of water may form hydroxide in the presence of hydride resulting in ester cleavage at the elevated temperatures of 110 °C.²²³



Scheme 3-1. Schematics of routes att. (a) Attempts to protect a phenol-sulfonate; (b) Alternative route involving the protection of an 4-iodo-benzylsulfonyl chloride to allow for subsequent sonogashira coupling. Conditions: (i) thionyl chloride, DCM, 80 °C; (ii) neopentyl alcohol (NeoOH), 1,4-diazabicyclo[2.2.2]octane (DABCO), 0 °C-r.t. (iii) NeoOH, DABCO, DCM, r.t.; (iv) 1-butyne-4-ol, Pd(PPh₃)₂Cl₂, CuI, PPh₃, i-Pr₂NH, toluene, 60 °C, 3 days; (v) NaH, DMF, 110 °C, 18 hours.

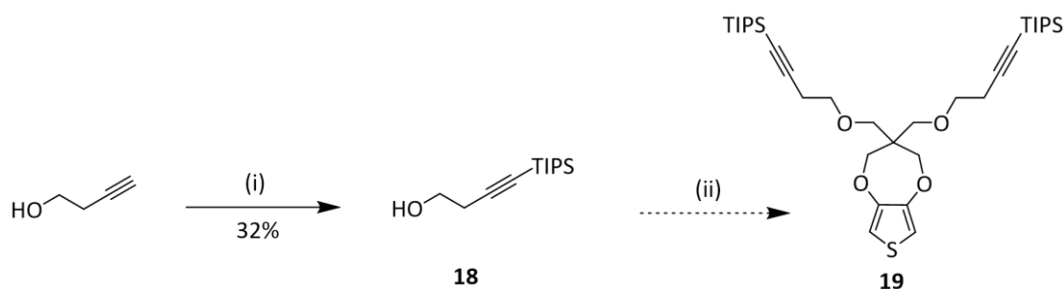
To avoid this issue, it was felt that installation of the alkyne onto the ProDOT derivative *followed by* Sonogashira of the protected sulfonate directly onto the ProDOT might avoid such deleterious side reactions. Initial attempts (**Scheme 3-2**) using 3-butyne-1-ol appeared to suffer from an intramolecular side reaction whereby a cyclic strained alkyne was inadvertently formed through the deprotonation of the alkyne's terminal CH. Repeats of this reaction using proportionally more of the alcohol and less hydride to encourage preferential hydroxyl deprotonation (although either could easily occur with H⁻

compare pK_a : alcohol = 17, alkyne = 25 and hydride = 35)²²⁴ were met with the same intramolecular bond formation. Clearly the global deprotonation of both functional groups in 3-butyne-1-ol coupled with the localisation of the bound reactive group precluded any significant di-substitution. Use of the weaker base potassium *tert*-butoxide (pK_a = 17) for preferential -OH deprotonation also failed to provide the DP. The reasons for this are currently unclear but could be due to it being an insufficient base for this particular alcohol.



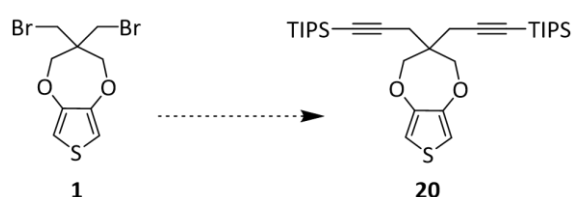
Scheme 3-2. Scheme of ProDOT functionalisation with an alkyne. Conditions: NaH or KOtBu, 1-butyne-4-ol, DMF, 110 °C, 18 hours.

Another attempted work around involved the triisopropylsilane (TIPS) protection of butynol prior to hydride installation on the ProDOT (**Scheme 3-3**). After successful protection for **18**, the use of NaH again resulted in a crude containing large amounts of polar (likely degraded) material with the possibility of a small amount of mono-substituted product. TIPS, and indeed silyl protecting group more generally, is most commonly cleaved in the presence of a fluoride anion that is able to insert itself through d-orbital hybridisation forming a pentavalent intermediate and subsequent liberation of the alkyne or alcohol.²²⁵ Though to the best of our knowledge there is no literature precedent for hydride cleavage of silyl protecting groups, this small anionic species may well function in a similar manner to the fluoride. However, more likely is the *in situ* generation of hydroxide from water in the solvents that might cause deprotection. More care in keeping dry conditions may thus be required.



Scheme 3-3. Scheme for installation of a protected alkyne onto ProDOT. Conditions: Ethylmagnesium chloride, triisopropylchloride, THF, Reflux, 18 hours; (ii) **18**, **1**, NaH, DMF, 110 °C, 18 hours.

Subsequent efforts were therefore made to circumnavigate this undesired side reaction through nucleophilic substitution of TIPS-acetylene in the presence of *n*-butyllithium to give **20** (**Scheme 3-4**). Despite numerous attempts however NMR suggested only mono-substitution was possible at best, this thought to be due to the sterically hindered nature of the nucleophile onto an already sterically crowded ProDOT substrate.



Scheme 3-4. Alkyne installation through substitution with TIPS acetylene. Conditions: TIPS-acetylene, *n*-BuLi, THF, -78 °C – r.t., 18 hours.

The investigation is ongoing and strategies such as lower reaction temperatures will be considered to slow the kinetics and prioritise the deprotonation of just the alcohol in 3-butyne-1-ol.

Despite difficulties in derivatising ProDOT with an alkyne, NaH was used to create nucleophilic centres (conditions from **Scheme 3-2**) that reacted with the bis(bromo methyl) substrate, **1**, to yield a range of ProDOT derivatives presenting a range of functional options (**21a** and **b**). As shown in **Figure 3-2**, this included ethyl and ethylene glycol derivatives to be used as a less sterically hindered spacers in subsequent polymers. It was found to push the reactions from mono- to di-substitution an excess (>5 eq.) of hydride and requisite alcohol was often required. Unfortunately, as will be discussed in the following section, in our hands this particular route was unable to produce diol derivatives.

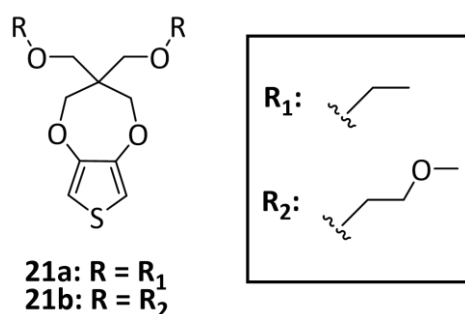


Figure 3-2. Other ProDOT derivatives synthesised through NaH-assisted S_N2

3.3.1.2 - Alcohol-functionalised ProDOT as a nucleophilic centre

Another avenue of interest was functionalising PEDOT derivatives in such a way that they might be printed. The growing expertise in the group to 3D print ever smaller feature sizes with polymers such as poly(ϵ -caprolactone) (PCL) could allow for PEDOT-based structures of exceptional intricacy to be produced that would in turn allow for complex and conductive micro-morphologies to be tested in cell studies. Growing a polymer like PCL from the periphery of a PEDOT derivative would hopefully allow for such materials to be produced. To initiate a process such as PCL polymerisation, a source of nucleophilicity was required and although hydroxy-methyl-EDOTs were available, the greater stability when brominated and possibility of two functional handles made ProDOT a more attractive option. A hydroxyl group would then allow for ring opening polymerisations of polyesters such as PCL using established protocols.²²⁶

Initial attempts were done using established literature protocols to acetylate and deprotect **4** to give ProDOT furnished with hydroxyl groups. However, concerns over the solubility and handle-ability of the subsequent polymers led to the pursuit of ProDOT derivatives with an extended chain linking it to the alcohol. Use of 1,8-octanediol in the standard NaH conditions was therefore explored.

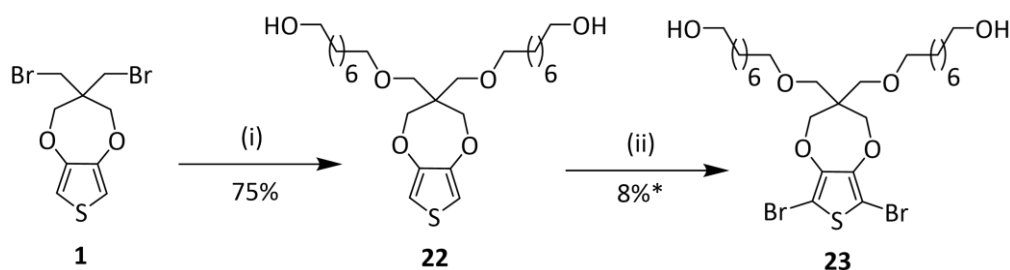
To achieve a high yield for this molecule, a number of conditions were therefore profiled in order to assess their efficacy at installing a 1,8-octanediol onto a ProDOT derivative to give ProDOT(C8-OH)₂ (**21**). Literature precedent and discussions with other chemists informed the reagent choice, with the resulting conditions being outlined in **Table 3-1**.

Table 3-1. Table of the conditions explored in generating a octanol-ProDOT derivative. Na HMDS = Sodium bis(trimethylsilyl)amide

Experiment No	Base	Solvent	Product seen	Yield
1	NaH	DMAc	No	-
2	NaH	DMF	No	-
3	KO ^t Bu	DMF	Yes	75%
4	Na metal	DMF	Yes	Trace
5	Na HMDS	DMF	Yes	4%

As can be seen, use of potassium *tert*-butoxide was able to produce the desired product in acceptable yield. It is worth noting this base was subsequently successfully employed for other ProDOT

derivatives such as a ProDOT(TG) (see chapter 2). The brominated product of ProDOT(C8-OH)₂, **22**, was readily achieved (**Scheme 3-5**) with standard conditions allowing its utility in a direct arylation polymerisation.



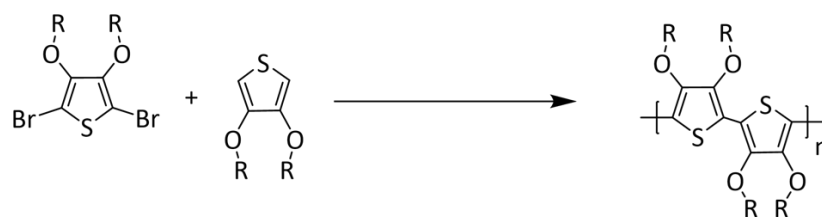
Scheme 3-5. Scheme for fabrication of a ProDOT derivative with pendant hydroxyl groups. Conditions: (i) 1,8-octanediol, KO^tBu, DMF, 110 °C; (ii) NBS, CHCl₃, r.t. *Note this yield was likely much higher since leaving the compound in ambient conditions caused polymerisation, using up a large portion of the yield.

Many similar narratives were experienced in the pursuit of functional EDOT/ProDOT derivatives and indeed only a subset are discussed here. From this point the attempts to incorporate such monomers into polymers through direct (hetero)arylation polymerisation (DHAP) will be presented.

3.3.2 - Polymer derivatives

3.3.2.1 - Functional PEDOT derivatives for organic electrochemical transistor (OECT) applications

Whilst the use of PEDOT:PSS in organic electrochemical transistor settings is well established, the PEDOT backbone often lacks sites of functionality to attach, for instance, biomolecules of interest that might modify the electronic response and act as a sensor. To this end, derivatives that include functional handles were explored to be used in collaboration with others in the group. The polymerisation conditions of choice are the direct (hetero)arylation polymerisation (DHAP) route previously explored by Reynolds group.⁶⁵ As such the required monomers were either purchased or synthesised and polymerised as shown below in **Scheme 3-6**.



Scheme 3-6. General schematic of the DHAP polymerisation. R here can be rings for a range of EDOT and ProDOT derivatives. Conditions: palladium(II) acetate, pivalic acid, potassium carbonate, DMAc, 140 °C.

Given the literature precedent for ProDOT-based OECT materials a system was designed that incorporated hydrophilic triethylene glycol monomethyl ether (TEGME) side chains and a functional handle. The former was included to allow penetration of aqueous mixtures into the bulk of the material, and not just the surface, thereby improving device performance and the latter was to act as a site of bioconjugation. As shown in the structure of P(TG)-P(N3) in **Figure 3-3**, an azide was selected as one option of functionality given its orthogonality to biochemical reactions. Simultaneously another polymer was designed bearing a hydroxyl moiety to expand the options the collaborator would have when selecting modes of bioconjugation.

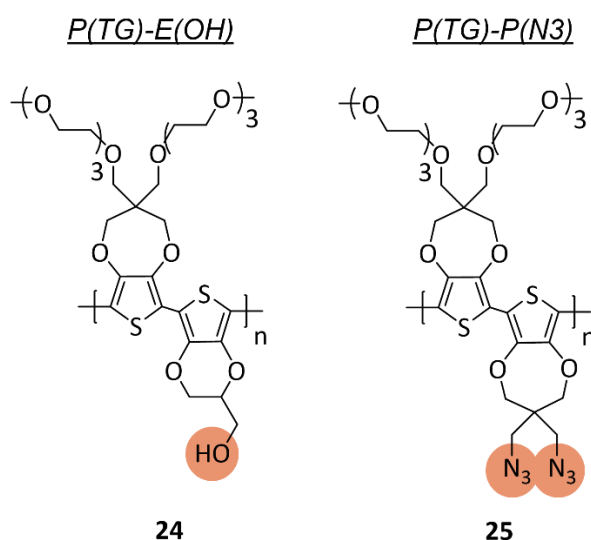


Figure 3-3. Polymers synthesised for OECT applications containing functional groups accessible for biomolecule conjugation.

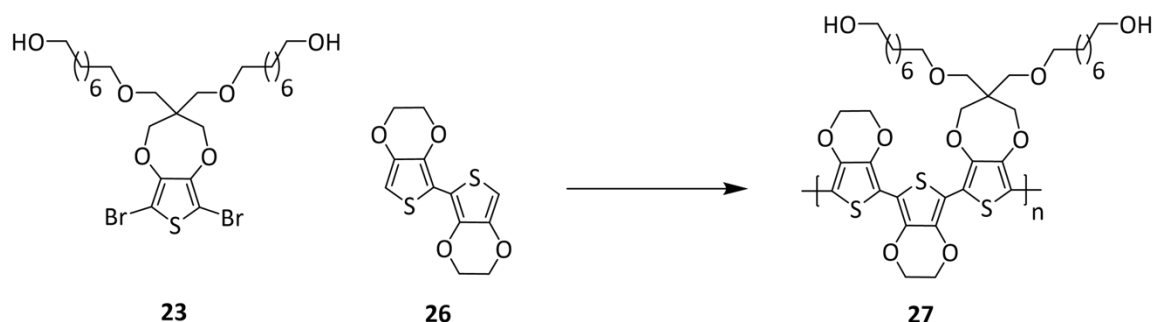
Initial efforts to synthesise these polymers were met with low yields and molecular weights below 5 kDa by MALDI-TOF. Long polymer chains are not necessarily crucial for this work since conjugation is naturally broken through backbone twisting and the density of moieties for bioconjugation will be the

same regardless. However, the low yields were troubling, and efforts are underway to improve these through ensuring purity of reagents and larger scale reactions to reduce any weighing errors. Additionally, peak broadening made the NMRs difficult to characterise and so full chemical characterisation is ongoing. Analysis using matrix assisted laser absorption/ionisation time of flight mass spectroscopy (MALDI-ToF) showed that whilst lower molecular weights precipitated into methanol (2-4 kDa), the methanol soluble crude contained higher molecular weights up to 8 kDa. It appears the ethylene glycol side chains increase methanol solubility at higher molecular weights and therefore other purification routes such as different solvents for precipitation and size exclusion columns will be considered moving forward.

3.3.2.2 - Functional PEDOT graft polymers as processable derivatives

Given the growing expertise in the group around 3-dimensional printing of intricate structures with micron-level resolution, printable derivatives have been simultaneously pursued. The polymer chemistry used in this case is identical to the OECT work given its precedent in the literature.^{64,65} The polymers were designed to contain moieties capable of functionalisation. Hydroxyl groups were chosen as a potential site of nucleophilicity since they can initiate the polymerisation of species such as poly(ϵ -caprolactone) (PCL). The designed polymers are presented below in **Figure 3-4**.

Early attempts utilised the brominated ProDOT(C8-OH) monomer previously synthesised, **23**, as shown in **Scheme 3-7**. Unfortunately, such efforts were met with significant solubility issues when copolymerised with BiEDOT, **26**.



Scheme 3-7. Scheme showing the synthesis of a hydroxyl-functionalised PEDOT derivative. Conditions: Palladium(II) acetate, pivalic acid, DMAc, 140 °C.

Since side chain solubility was required from one of the co-monomers, it was reasoned one should be less sterically imposing to reduce any deleterious impact on the conjugation length and hence charge transport properties. Further, EDOT derivatives are difficult to brominate since they readily polymerise and as such should ideally be left as the non-brominated comonomer. Therefore, the design was shifted such that the hydroxyl group was found on an EDOT monomer, a molecule that is commercially available.

As such the polymers presented in **Figure 3-4** were synthesised. These were hoped to exhibit significant solubility from the branched alkyl side chains yet display the desired hydroxyl functionality. While PE-OH (**29**) is a simple copolymerisation between an alcohol-bearing EDOT monomer, PE2-OH (**28**) incorporates a 1:1 ratio of BiEDOT:Hydroxymethyl-EDOT in a bid to extend conjugation and increase charge transport.

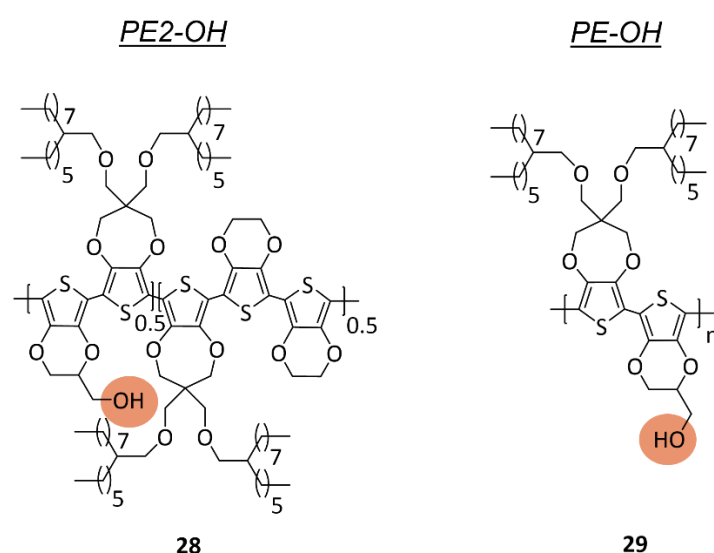


Figure 3-4. Polymers synthesised with pendant hydroxyl groups as sites of initiation for poly(ϵ -caprolactone) (PCL) growth. Highlighted: the pendant hydroxyl functionality.

Purification was undertaken using standard Soxhlet procedures (washed using methanol, acetone, and hexanes) with the final CHCl_3 wash assumed to contain the highest molecular weight fractions.⁶⁵ Despite the substantial side chains, after drying the CHCl_3 fractions were still difficult to re-dissolve even with ultrasonication. It was postulated this might be a result of slow doping in air by triplet oxygen species as was seen for the design 1.0 polyesters in Chapter 2. It has generally been observed with all polymers attempted that use of a de-doping reagent, in this case the base triethylamine (Et_3N), both increases the solubility and changes the solution colour. Investigating the absorption and emissive properties revealed some notable changes. As shown in **Figure 3-5a** addition of base

completely erases longer wavelength bands indicating they originate from polaronic species present in the doped state. A blue shift is also seen upon addition of Et_3N from 330 – 290 nm indicating depopulation of a state just within the bandgap. A possible source of both the 590 nm and 330 nm peaks might be promotion to and from polaronic ($+1e$) or bipolaronic ($+2e$) bands.¹⁹⁷ Unfortunately such a short wavelength peak after de-doping implies either only small oligomers or a short conjugation length brought about by excessive backbone twisting, perhaps due to too much steric hinderance from the peripheral alkyl chains. Such an observation was also found by GPC and MALDI-ToF with molecular weights only up to a maximum of 5 kDa implying only oligomeric species. Either case would limit the charge transport properties of the resulting material and as such the polymerisation will need to be repeated with care taken as to the purity of the reagents and weighing errors the latter of which can be minimised by larger scale reactions.

Examination of **Figure 3-5b** reveals a similar erasure of a longer wavelength emission peak (~ 625 nm) in the case of PE-OH again indicating removal of these polaronic states. Curiously, although the same 625 nm peak vanishes, upon application of base PE2-OH showed the increase of a longer wavelength emission band at around 525 nm. It is possible de-doping the backbone altered chain conformation such that a previously forbidden radiative decay pathway became activated, a feature that is introduced by the presence of the likely more planar BiEDOT comonomer (**26**).

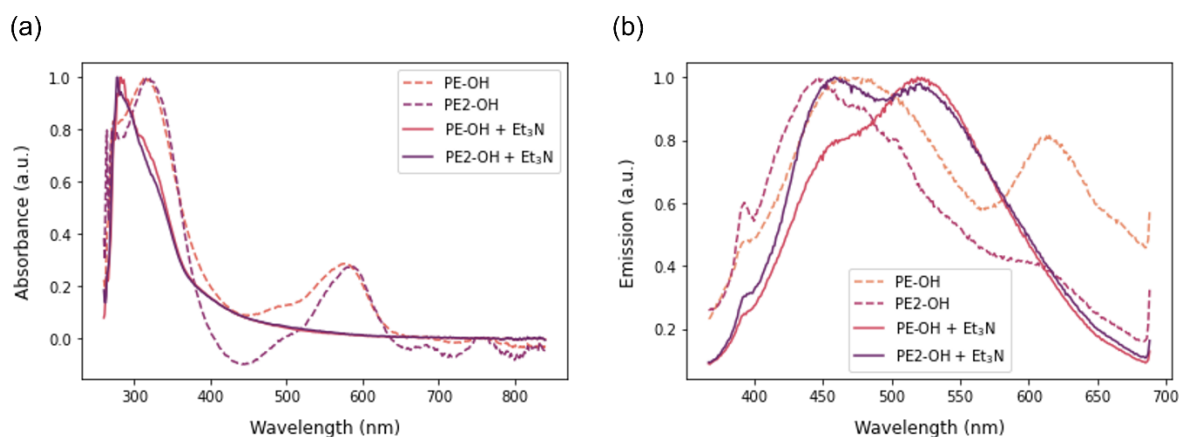


Figure 3-5. Normalised data for (a) UV-vis absorption profiles of the highest M_w fractions from PE2-OH and PE-OH synthesis. Addition of Et_3N appears to erase the longer wavelength bands in both cases; (b) Photoluminescence emission spectra of PE-OH and PE2-OH before and after the addition of triethylamine. Excitation at 350 nm, all spectra recorded at concentrations between 0.2-0.4 mg/ml.

Cyclic voltammetry (CV) of the polymers is shown in **Figure 3-6** and estimated highest molecular orbital (HOMO) energies of -4.35 eV and -4.6 eV for PE2-OH and PE-OH respectively. It appears the inclusion of a BiEDOT unit promotes 1 electron oxidation of the backbone. The reduced oxidation potential with increased EDOT content is in line with previously published work⁶⁵ and is thought to originate from increased ability to planarise through less steric hinderance from side chains and bulkier dioxy rings. For reference, the HOMO level for pure PEDOT is found to be around -3.3 eV⁶⁵, indicating how the trend in lowering oxidation potential proceeds with increasing EDOT content.

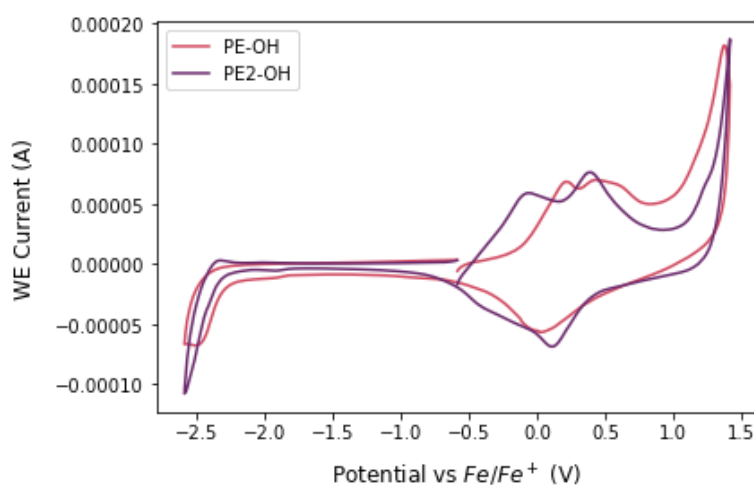


Figure 3-6. Cyclic voltammetry (CV) of PE-OH and PE2-OH.

Subsequent MALDI-ToF experiments have indicated molecular weights only up to 4 kDa for both polymers confirming them as oligomeric. Despite this, initial attempts have been made to polymerise poly(ϵ -caprolactone) (PCL) off the backbone. At present the NMR data is inconclusive as to whether the PCL is polymerising from the backbone or from possible traces of water in the reaction, confirming this will require the use of complementary techniques such as diffusion-ordered NMR spectroscopy (DOSY NMR), GPC, MALDI-ToF and fluorescence correlation spectroscopy (FCS), work that is currently in progress.

3.4 - Conclusions and future work

A selection of synthetic challenges around the functional derivatisation of EDOT/ProDOT have been discussed with a range of novel functional monomers being produced. Where obstacles have been

encountered, possible rationale has been offered and synthetic work-arounds suggested and often executed. With this growing library of functional monomers, polymers for collaborative projects in several areas of conductive polymer application have begun to be synthesised and characterised.

Polymers have been designed and synthesised for OECT applications with functional handles for bioconjugation. Efforts are currently underway to improve the yields and molecular weights of the materials. From this point, after full characterisation the polymers can be tested in an OECT setting through collaboration with others in the lab.

In the pursuit of printable conductive polymers through insertion of a nucleophilic centre onto a PEDOT derivative, preliminary polymers have been produced and optoelectronically characterised. The data suggests these materials may still be oligomeric and require further optimisations in the polymerisation protocol with fresh reagents and at larger scales to reduce weighing errors. Some efforts have been made in attempting polymerisation of poly(ϵ -caprolactone) from the pendant hydroxyl groups but at present data is inconclusive as to how successful this is. Looking forward, PE-OH and PE2-OH polymers of higher molecular weight as well as other hydroxyl-based variations that potentially incorporate ProDOT(C8-OH)₂, will be pursued. With these in hand further optimisation of the PCL growth step will be explored and other techniques such as diffusion-ordered NMR spectroscopy (DOSY NMR) and fluorescence correlation spectroscopy (FCS) will be considered to ascertain PCL growth from the PEDOT derivative. Given the expertise present in the group with printing of semiconductor-PCL brush copolymers, it is hoped demonstrating printability with these systems will be achievable after which appropriate cytotoxicity studies will be considered.

3.5 - Experimental

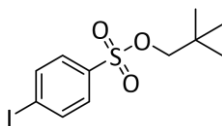
All details not included here regarding material and characterisation can be found in the general experimental section of Appendix I.

3.5.1 - Synthesis

Several compounds have already been detailed experimentally in Chapter 2 and so their synthesis is not outlined here. Br₂ProDOT(C8OH)₂ (**23**) was synthesised by James Foote.

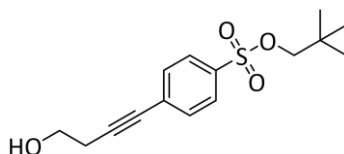
3.5.1.1 - Small molecules

I-BS-Neo: neopentyl 4-iodobenzenesulfonate (**14**)



To a 100 mL RBF was added iodobenzylsulfonyl chloride (1.47 mmol, 1 eq.) and anhydrous DCM (20 mL). To this was added neopentyl alcohol (1.61 mmol, 1.1 eq.), the mixture purged with nitrogen and placed in an ice bath. Separately, DABCO (1.91 mmol, 1.3 eq.) was dissolved in anhydrous DCM (5 mL) and slowly added dropwise to the mixture. This was allowed to warm to room temperature and stirred gently for 2.5 hours. The material was purified on a silica flash column using 40-60% DCM in Hexanes giving the desired product in a 71% yield. ^1H NMR (400 MHz, CDCl_3): δ = 7.85 (2H, d, I-C-CH, J = 8.5 Hz), 7.55 (2H, d, S-C-CH, J = 8.7 Hz), 3.60 (2H, s, tBu-CH₂), 0.70 (9H, s, C-(CH₃)₃). ^{13}C NMR (75 MHz, CDCl_3): δ = 138.58, 129.24, 128.16, 101.44, 80.04, 31.77, 26.07 LRMS m/z ESI+: Calc: 353.98 Found: 355.1 [M+H]⁺

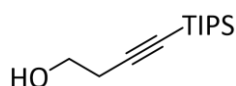
Bu-BS-Neo: neopentyl 4-(4-hydroxybut-1-yn-1-yl)benzenesulfonate (**15**)



To a 25 mL RBF was added the iodobenzylsulfonate neopentyl ester (0.596 mmol, 1 eq.), CuI (0.0119 mmol, 0.02 eq.), and PPh_3 (0.0238 mmol, 0.04 eq.). This was followed by charging under N_2 and, with the assistance of a nitrogen blanket, the careful addition of $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (0.0119 mmol, 0.02 eq.). To this was then added anhydrous toluene (~5 mL) and $i\text{-Pr}_2\text{NH}$ (1 mL) and the mixture degassed with an N_2 balloon for around 10 minutes. Simultaneously, the 3-butyne-1-ol (0.715 mmol, 1.2 eq.) was dissolved in anhydrous toluene (~5 mL) in a rubber stopper-sealed 27 mL vial and degassed for around

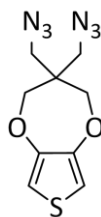
10 minutes also. The latter was added slowly to the former and mixture heated to 60 °C and stirred for 3 days. Mixture was diluted with Et₂O and filtered through celite. This was concentrated for use immediately on a silica column. Column dry loaded (some residual toluene after Et₂O removal was azeotroped away with methanol to give powder-like silica ready for dry loading) and eluted with 100% DCM on a flash silica column giving the desired product in a 71% yield. ¹H NMR (400 MHz, CDCl₃): δ = 7.80 (2H, d, C-C-CH), 7.53 (2H, d, S-C-CH), 3.81 (2H, t, HO-CH₂), 3.67 (2H, s, tBu-CH₂), 2.68 (2H, t, HO-CH₂-CH₂), 0.88 (9H, s, -C-(CH₃)₃). ¹³C NMR (75 MHz, CDCl₃): δ = 134.74, 132.56, 129.41, 128.64, 128.06, 91.57, 81.12, 79.66, 60.67, 31.85, 25.59, 24.01. LRMS *m/z* ESI+: Calc: 296.11, desired product did not seem to fly with electrospray.

TIPS-butynol: 4-(triisopropylsilyl)but-3-yn-1-ol



To a solution of 3-Butyne-1-ol (5.28 mmol, 1 eq.) dissolved in THF was added ethylmagnesium chloride (11.1 mmol, 2.1 eq.) over around 30 minutes at room temperature. This was refluxed for 12 hours following which the reaction was cooled to room temperature and triisopropylchlorosilane (5.28 mmol, 1 eq.) in THF was added over 15 minutes. This was again refluxed this time for 6 hours. The reaction was cooled to room temperature, carefully poured into 10% HCl, extracted with Et₂O twice, MgSO₄ dried, filtered and concentrated for a flash column. The column was run in a 30-100% EtOAc in hexanes gradient giving the desired product with 32% yield.²²⁷ ¹H NMR (400 MHz, CDCl₃): δ = 3.69 (2H, t, HO-CH₂, J = 6.4 Hz), 2.50 (2H, t, HO-CH₂-CH₂, J = 6.4 Hz), 1.05 (3H, br, -Si-CH), 1.13 – 0.9 (18H, m, -Si-CH-CH₃).

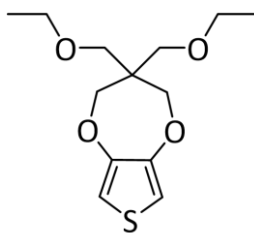
ProDOT(N3): 3,3-bis(azidomethyl)-3,4-dihydro-2H-thieno[3,4-b][1,4]dioxepine



Compound was prepared by James Foote according to and NMR consistent with previous literature protocols with a yield of 98%.²²⁸ ^1H NMR (400 MHz, CDCl_3): δ = 6.50 (2H, s), 3.91 (4H, s), 3.51 (4H, s).

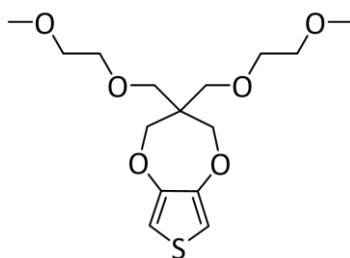
General protocol for nucleophilic substitutions onto **1**. To a 100 mL RBF was added NaH (4 eq.), the requisite alcohol (5 eq.), a stirring bar and charged under nitrogen. This was dissolved in DMF and heated to 110 °C for 30 minutes following which the mixture was cooled to room temperature, **1** (1 eq.) added under a positive nitrogen atmosphere and the mixture again heated to 110 °C this time overnight. After this time the reaction mixture was cooled to room temperature was quenched by stirring with $^i\text{PrOH}$ for 30 minutes. All solvent was then evaporated off by drying under nitrogen flow after which the mixture was extracted using DCM and water, washed twice with deionised water, once with brine, dried with MgSO_4 , filtered and concentrated *in vacuo*. Flash column chromatography was then undertaken.

ProDOT(OEt)₂: 3,3-Bis(ethoxymethyl)-3,4-dihydro-2H-thieno[3,4-b][1,4]dioxepine (**21a**)



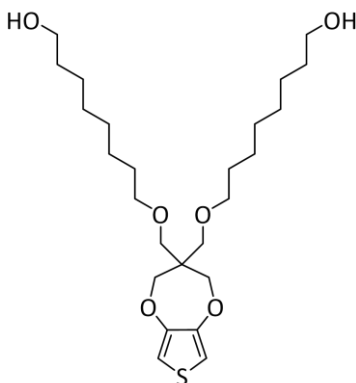
Purified using 30% DCM in Hexanes. ^1H NMR (400 MHz, CDCl_3): δ = 6.43 (2H, s, -S-CH), 4.00 (4H, s, -O-CH₂ (dioxo ring)), 3.49 (4H, s, C-CH₂), 3.46 (4H, q, -O-CH₂-CH₃), 1.16 (6H, t, -O-CH₂-CH₃). ^{13}C NMR (75 MHz, CDCl_3): δ = 149.82, 105.20, 73.84, 69.49, 67.06, 47.60, 15.10, 14.25, 14.20. LRMS m/z ESI⁺: Calc: 272.11 Found: 273.1 [M+H]⁺

ProDOT(EG)₂: 3,3-Bis((2-methoxyethoxy)methyl)-3,4-dihydro-2H-thieno[3,4-b][1,4]dioxepine (**21b**)



Column run in 30-100% DCM in Hexanes. ^1H NMR (400 MHz, CDCl_3): δ = 6.43 (2H, s, -S-CH), 4.01 (4H, s, -O-CH₂ (dioxo ring)), 3.58 (4H, m, -O-CH₂-CH₂-OMe), 3.56 (4H, s, C-CH₂), 3.50 (4H, m, -O-CH₂-CH₂-OMe), 3.35 (6H, s, -O-CH₃). ^{13}C NMR (75 MHz, CDCl_3): δ = 149.78, 105.31, 73.65, 71.83, 71.15, 70.20, 59.09, 47.89. LRMS m/z ESI+: Calc: 332.13 Found: 333.1 $[\text{M}+\text{H}]^+$, 355.0 $[\text{M}+\text{Na}]^+$.

ProDOT(C8OH): 8,8'-(((3,4-dihydro-2H-thieno[3,4-b][1,4]dioxepine-3,3-diyl)bis(methylene))bis(oxy))bis(octan-1-ol) (**22**)



As described in the main text, with the help of James Foote a variety of conditions were employed to synthesise ProDOT(C8OH). In general, to a microwave vial was added a stirring bar, the required base, diol and crown ether (see main text). This was dissolved in 2.5 mL of the required solvent (see main text) and stirred for 45 minutes at 110 °C. After cooling to room temperature the ProDOT(CH₂Br)₂ was added in 2.5 mL of the chosen solvent and the reaction stirred overnight at 110 °C. Reactions were monitored by TLC and when deemed complete were quenched with 2-propanol at room temperature for 30 minutes. The reactions were then dried in vacuo, diluted in DCM and washed with

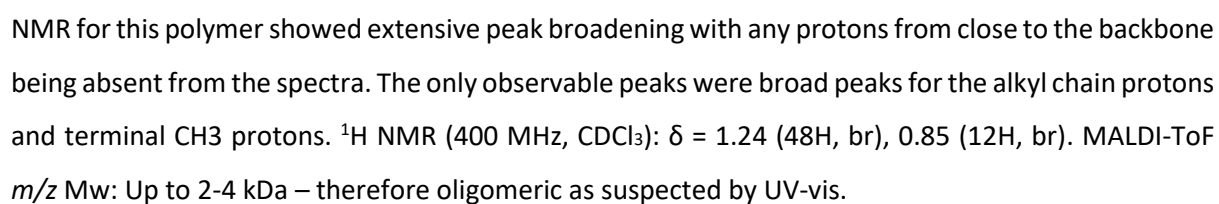
water then brine. Purification was then typically carried out by going from 100% DCM to 100% EtOAc on a silica flash column. Using KO^tBu as a base and DMF as a base gave a yield of 75%. ¹H NMR (400 MHz, CDCl₃): δ = 6.44 (2H, s, -S-CH), 4.00 (4H, s, -O-CH₂ – of dioxy ring), 3.64 (4H, t, CH₂-OH), 3.47 (4H, s, -C-CH₂-O-) 3.39 (4H, t, -O-CH₂-CH₂-), 1.55 (8H, br, -O-CH₂-CH₂- and -CH₂-CH₂-OH), 1.31 (16H, br, alkyl protons).

3.5.1.2 - Polymers

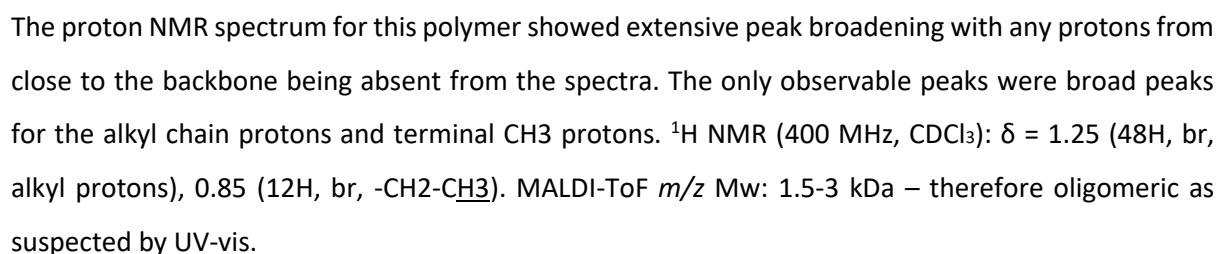
3.5.1.2.1 - General procedure

The procedure for polymerisation followed established direct (hetero)arylation polymerisation procedures.⁶⁵ In general, to a 5 mL microwave vial was added the requisite comonomers (two of Br2ProDOT(TG), ProDOT(N3), EDOT-OH, Br2ProDOT(HD)) (1 eq. each), Pd(OAc)₂ (2 mol %), pivalic acid (0.3 eq.), potassium carbonate (2.5 eq.) and a stirring bar. The vial was sealed under argon and DMAc (*N,N*-dimethylacetamide – anhydrous) added (~5 mL). After stirring for 2 minutes the mixture was heated to 140 °C and stirred overnight. Following this the mixture was poured into cold methanol, stirred for 1 hour and the precipitate filtered into a cellulose thimble. The thimble was then washed using a Soxhlet extractor with methanol, acetone, hexanes and finally the remaining material in the thimble dissolved in chloroform. The chloroform was removed under reduced pressure yielding an often blue/purple solid.

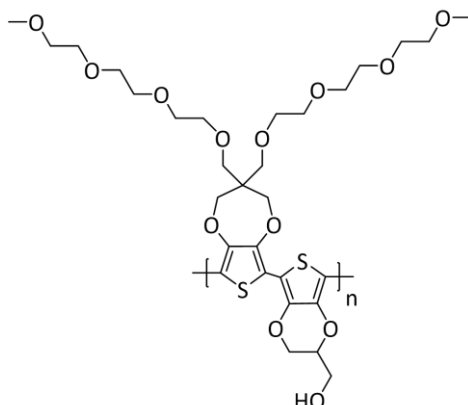
P(HD)-E2-E(OH): Poly(7-(3,3-bis(((2-hexyldecyl)oxy)methyl)-8-methyl-3,4-dihydro-2H-thieno[3,4-b][1,4]dioxepin-6-yl)-7'-methyl-2,2',3,3'-tetrahydro-5,5'-bithieno[3,4-b][1,4]dioxine-*stat*- (5-(3,3-bis(((2-hexyldecyl)oxy)methyl)-8-methyl-3,4-dihydro-2H-thieno[3,4-b][1,4]dioxepin-6-yl)-7-methyl-2,3-dihydrothieno[3,4-b][1,4]dioxin-2-yl)methanol)



P(HD)-E(OH): Poly((5-(3,3-bis(((2-hexyldecyl)oxy)methyl)-8-methyl-3,4-dihydro-2H-thieno[3,4-b][1,4]dioxepin-6-yl)-7-methyl-2,3-dihydrothieno[3,4-b][1,4]dioxin-2-yl)methanol)



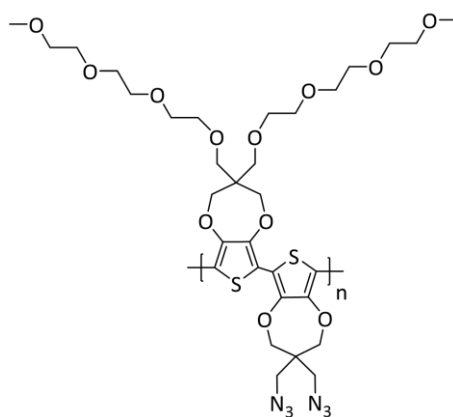
P(TG)-E(OH): Poly((5-(3,3-di(2,5,8,11-tetraoxadodecyl)-8-methyl-3,4-dihydro-2H-thieno[3,4-b][1,4]dioxepin-6-yl)-7-methyl-2,3-dihydrothieno[3,4-b][1,4]dioxin-2-yl)methanol)



The proton NMR spectrum (see appendix III) showed some evidence of ethylene glycol. Bad signal to noise ratio and peak broadening. Too little material was obtained to assign any carbon peaks. The following assignments are therefore quite uncertain. ^1H NMR (400 MHz, CDCl_3): δ = 4.32 (5H, br, EDOT dioxy ring protons), 3.63 (32H, br, triethylene glycol and all ProDOT dioxy ring protons).

MALDI-ToF m/z Mw: 2-4 kDa in MeOH precipitate, 6-8 kDa in reaction crude.

P(TG)-P(N3): Poly(3,3-bis(azidomethyl)-3',3'-di(2,5,8,11-tetraoxadodecyl)-8,8'-dimethyl-3,3',4,4'-tetrahydro-2H,2'H-6,6'-bithieno[3,4-b][1,4]dioxepine)



The proton NMR spectrum (see appendix III) showed some evidence of ethylene glycol. Bad signal to noise ratio and peak broadening engulfed all protons (both starting materials had signals only around 3-4 ppm region). Too little material was obtained to assign any carbon peaks. The following assignments are therefore quite uncertain. ^1H NMR (400 MHz, CDCl_3): δ = 3.66 (40H, br, triethylene glycol and all ProDOT dioxy ring protons). MALDI-ToF m/z Mw: 2.5-4 kDa, 4-6 kDa in reaction crude.

Chapter 4 - Design and characterisation of 3,4-ethylenedioxythiophene supramolecular hydrogels

4.1 - Introduction

In previous chapters, the potential of oligo-3,4-ethylenedioxythiophene (EDOT) structures in degradable polymeric structures has been explored as an alternative to conventional formulations of PEDOT in the field of bioengineering. This is, however, not the only pathway to biocompatible and bio-resorbable materials based on conductive polymers. Low molecular weight gelators (LMWGs) have shown increasing promise in recent years as ideal soft materials for use in bioengineering applications. It was therefore speculated as to whether oligo-EDOT moieties might be incorporated into such systems allowing for the synergy of the appropriate mechanical and biocompatible properties found in LMWGs with the charge transport characteristics shown by these conjugated segments. It was further imagined that well-defined ordering and assembly might bring EDOT oligomers near or into direct contact with one another, substantially increasing intermolecular charge transport and allowing for precise control of both the separation and orientation of the π -bonded components. In this chapter EDOT-based supramolecular hydrogels are demonstrated with extensive structure-property characterisation through a range of techniques including rheology, atomic force microscopy (AFM), UV-vis and PL spectroscopy, pH profiling and small angle x-ray scattering (SAXS). Three different EDOT-capped peptide sequences were found to produce hydrogels, with a flexible glycine unit proving key in generating gels of the greatest storage modulus.

4.2 - Background

Low molecular weight gelators leverage the innate assembling capacity of short peptide sequences to construct well defined fibre geometries that in turn entangle, trap water and ultimately form hydrogels. The material class originates from studies of supramolecular systems in nature such as amyloid polypeptides where key motifs of self-assembly were identified and mimicked.²²⁹ From here

the field has rapidly expanded to create ever more complex and functional hydrogel systems.¹⁶⁹ The identity of the N-terminus capping group has been modulated extensively with particular contributions in understanding their assembly and scope coming from the Adams, Draper, Gazit and Ulijn laboratories. As mentioned previously, capping group identities include pyrene,¹⁷³ carbazole,¹⁷⁸ naphthalene,^{180,230} anthracene, phenanthrene and, in particular, fluorene.^{173,231} Many of these examples have provided systems capable of forming gels with less than 0.01% (w/v) gelator. Thiophene derivatives have also been explored in this context^{232,233} with work from Draper et al. demonstrating intriguing gel ageing whereupon a gel-to-gel transition yielded an opaque to clear transformation accompanied by an increased storage modulus.²³⁴ A number of reports exist exploring the optoelectronics and charge transport propensity of 1-dimensional supramolecular assemblies from small, conjugated molecules including porphyrins,²³⁵ perylenes,²³⁶ triphenyl amines and benzenetricarboxamides to name a few.²³⁷ Whilst innovative, fewer reports explore the optoelectronic and charge transport properties of gel systems formed of LMWGs, an avenue that should be readily accessible given the ease of appending conjugated moieties.

Some reports of charge diffusion and energy transfer in LMWG systems have begun to appear in recent years. An early example from Chen et al. demonstrated energy transfer from a naphthalene-capped di-phenylalanine (FF) donor to an anthracene-capped FF acceptor via co-assembly or to a hosted dansyl acceptor.²³⁰ Moving toward systems capped with oligomeric aromatic species, however, more complex and intricate examples can be found. The Tovar group in particular has pioneered synthetic routes to incorporate conjugated systems between two short peptide sequences showing remarkable optoelectronic and charge transport phenomena.^{238,239} For instance, using peptide dimers built in this fashion, co-assembling donor-acceptor systems could be demonstrated where just 1 mol % of the tetra-thiophene-core (4T) acceptor could quench the oligo-(*p*-phenylenevinylene)-core (OPV) donor photoluminescence emission by 47 %, a phenomena indicative of extensive exciton migration.²⁴⁰ Similarly, making 4T the donor, it was shown the acceptor, in this case naphthalene diimide, could be grafted from the peptide itself and energy transfer demonstrated.²³⁸ Notably, 4T has also demonstrated considerable charge transport properties with transistor architectures in which mobilities up to $0.02 \text{ cm}^2 \text{ V}^{-1} \text{ s}^{-1}$ were seen as a source-drain channel material and optimum function as gate electrode across distances of 35-40 nm implied ability to transmit electronic signals over substantial and biologically relevant distances.²⁴¹

Conductive LMWG systems have also been reported. One avenue involves leveraging a self-assembled network to trap electrolytes forming 'ionogels'.^{242,243} Such gels have been shown to exhibit significant ionic conductivity ($\sim 10^{-2} \text{ S/cm}$), but it is unclear how this might be maintained in a biological setting given the osmotic gradient that would exist. Another method involves the assembly of peptide capped

monomers that are subsequently polymerised after assembly. This has been demonstrated for thiophene and EDOT to form conductive, though likely non-degradable, gels.^{244,245}

Whilst intriguing there are, to the best of our knowledge, no examples of EDOT oligomer assembly for a truly supramolecular gel as a conductive biomaterial. Given the aim of this thesis to create novel variations of PEDOT for biomaterials, this was selected as an inviting avenue in which to explore the assembly potential of oligo-EDOT systems along with the mechanical, optoelectronic and charge transporting properties therein.

4.3 - Project aims and molecular design

The aims of this chapter are to elucidate the relationship between the structural design of EDOT-peptide systems and their self-assembling propensity. A range of techniques will be utilised to assess structurally what determines gel formation in EDOT-peptides, how and why they form as well as quantifying the mechanical and optoelectronic properties of the systems. Given its extensive exploration in the literature, a pH trigger was opted to trigger gelation whereby the solubility of the molecule would be decreased as a carboxylate functionality is protonated when the pH is lowered resulting in self-assembly. Furthermore, pH switches have been suggested to be superior in ascertaining if a molecule can form a gel compared to, for example, solvent switch triggers as some that gel with former do not with the latter.¹⁷³

The first step was therefore to select peptide sequences likely to yield hydrogels. The forces that will determine this will include: (i) the intermolecular hydrogen bonding; (ii) the hydrophobicity of the sequence that will in turn inform the aggregation propensity; (iii) the potential to form pi-pi interactions. Unsurprisingly, most sequences that successfully form hydrogels will include phenylalanine (Phe) since it offers all three of these. Indeed, in predictive studies previously undertaken, most sequences predicted to assemble contained at least one Phe moiety.²⁴⁶ It should be noted that whilst a certain amount of hydrophobicity is required for assembly, excessive hydrophobicity will likely cause random aggregation and precipitation. Although general design rules have been identified, it should be noted the field still lacks a precise theoretical framework to predict gelation of a given LMWG with even small, seemingly innocuous, changes in molecular structure precluding gel formation where previously there might have been. There are still no guarantees in the design process and as such the 'rules' stipulated previously should be viewed more as guidelines than hard facts.^{247,248}

Beyond Phe several other amino acids of interest were identified. Glycine (Gly) is a simple amino acid that has been incorporated in gel systems and is believed to add flexibility between the aromatic capping group of the N-terminus and the rest of the peptide system.²⁴⁹ This can be beneficial in allowing the molecules to rotate and pack more efficiently, encouraging assembly.¹⁷³ Another amino acid identified for investigation was aspartic acid (Asp). The presence of two carboxyl groups with differing pK_a values will have the effect of protonating sequentially as the pH decreases, which could provide a different path to possible assembly when compared to a similar peptide with a single carboxylic acid.²⁵⁰ Further, the presence of an additional carboxylic acid will aid solubility in basic conditions particularly when the aromatic capping groups become oligomeric, the ultimate aim of this work.

Considering all the factors mentioned, the target sequences outlined in **Table 4-1** were designed.

Table 4-1. Table outlining the sequences explored in this work. Unless specified all amino acids are in their L-isomeric form.

EDOT capping group	3-letter code	1-letter code
Mono-EDOT ('E1')	-Phe-Phe	-FF
	-Phe-Phe-Asp	-FFD
	-Gly-Phe-Phe	-GFF
	-Phe-Phe-Phe	-FFF
	-Gly-Phe-Phe-Asp	-GFFD

4.4 - Results and Discussion

4.4.1 - Synthesis of mono-EDOT peptides

The synthesis of mono-EDOT-peptides was carried out using conventional Fmoc solid phase protocols (see experimental section). This was combined with EDOT derivatisation previously published by our research group.¹⁹⁴ Full synthetic details can be found in the experimental section but suffice to say all 5 molecules were successfully synthesised and fully characterised as shown by NMR, HPLC and mass spectroscopy.

4.4.2 - Gelation ability of mono-EDOT peptides

To achieve homogenous gelation of the peptides, the technique of a gradual pH trigger using the slow hydrolysis of glucono- δ -lactone (GdL) was employed.²⁵¹ In brief the requisite EDOT-peptide was dissolved in an aqueous solution containing 1.5 equivalents of aqueous sodium hydroxide solution often with the aid of sonication. To this solution was then added 2 equivalents of GdL and the sample left overnight. As described in **Table 4-2**, E1FF and E1FFD resulted in precipitation after the solution was acidified with GdL. It was found that E1FFF, E1GFF and E1GFFD were all able to form gel-like materials by eye (**Figure 4-1**). Estimates were made of their minimum gel concentration (MGC) but it should be noted these include large uncertainty since only a vial inversion test was used at this point.

Table 4-2. Tabulation of the gel-forming (by eye) ability or lack thereof found in the mono-EDOT-peptide systems investigated.

EDOT-Peptide	Gel formation?	Description	Apparent MGC (mM)
E1FF	No	Precipitation with some gel-like behaviour at high (> 5 mM)	-
E1FFD	No	Precipitation	-
E1GFF	Yes	Cloudy gel	2.4
E1FFF	Yes	Translucent gel	1.2
E1GFFD	Yes	Cloudy gel	2.4

It seemed whilst diphenylalanine alone caused precipitation, insertion of a single glycine unit between FF and the EDOT allowed gelation to occur. Similarly, insertion of glycine into E1FFD to give E1GFFD also facilitated gelation. It is reasoned this was a result of the increased flexibility allowing the units to adopt the required shape for self-assembly.¹⁷³ The use of three phenylalanine units yielded the lowest minimum gel concentration (MGC) by eye, producing a translucent gel-like material as measured using a vial inversion test down to concentrations of around 1.2 mM. That said, it should be noted that a system exhibiting solid behaviour when composed of >99.9% water, as appears to be the case for E1FFF, have been described as ‘super-hydrogelators’.¹⁷⁸ Regarding the appearance of the gels, both E1GFF and E1GFFD appeared cloudy whilst E1FFF was translucent. This could suggest the presence of larger, possibly particulate aggregates in the former that are causing light scattering and could either imply the ordering and homogeneity of E1FFF is greater than its counterparts or that its assembly does not give morphologies capable of light scattering.

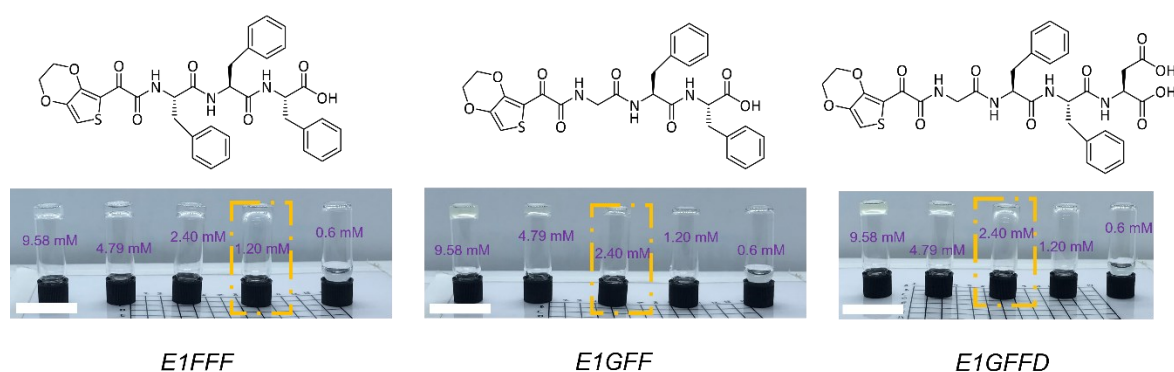


Figure 4-1. Vial inversion tests for the 3 sequences able to form gels and their corresponding chemical structures. Highlighted in orange are the minimum gel concentrations for this dilution series. Scale bar = 2 cm.

To assess the morphologies of the hydrogel fibres, atomic force microscopy (AFM) was employed. AFM is an ideal analysis technique for self-assembling systems owing to its operation in ambient conditions, minimal sample preparation/manipulation yet resolution to the nanometre scale. In addition, compared with electron microscopy techniques, the samples do not require staining which could introduce artifacts. It should be noted, however, that images are of the dried sample not the aqueous gel itself and so any stipulations as to what the true structure is in solution will assume that negligible structural changes occur upon depositing and drying the sample. For this reason, cryo-TEM is often employed in conjunction with AFM.

Imaging of E1FFF with AFM revealed an entangled fibrous network (**Figure 4-2a and b**) as seen previously in the literature with similar systems.¹⁶⁹ Analysis of the fibre diameter and distribution (**Figure 4-2c and d**) revealed an average fibre diameter at the 95% confidence interval of 4.8 ± 1.2 nm. Given the extended length of around 2 nm for the molecule itself it is possible the fibres are bi-molecular, i.e. formed of 2 adjacent LMWG molecules per stacking layer. This could result from a cylindrical micelle or disc-like structure the like of which has been probed extensively in the short-peptide gelator field.²⁵² It should be noted here that owing to tip broadening effects from the AFM the width can appear artificially wide hence the use of height in establishing a better estimate for fibre diameter. It is therefore assumed that the fibres are perfectly cylindrical.

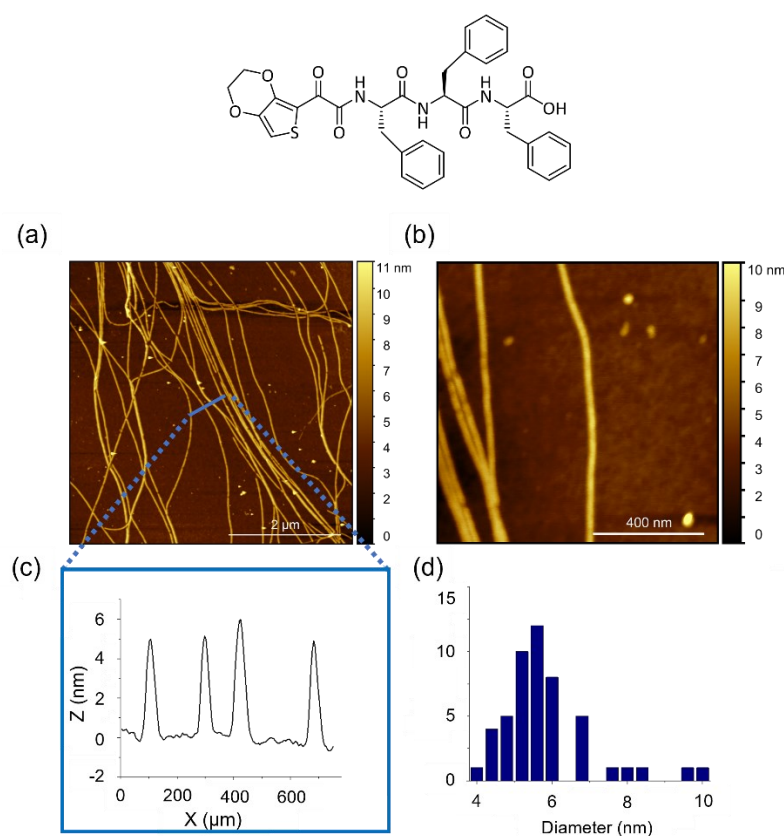


Figure 4-2. E1FFF was examined using AFM showing a system of entangled fibres (a) and (b), profile were extracted from these images using Gwyddion analysis software (c) and plotted in a histogram (d) – bin size = 0.4 nm, 50 measurements taken. From this data the fibre diameter was estimated to be 4.8 ± 1 nm.

Analogous measurements were carried out for E1GFF and E1GFFD yielding similarly entangled fibre architectures (**Figure 4-3a and b**). Histograms of both samples showed a broader distribution of fibre sizes (**Figure 4-3**) when compared to E1FFF. Whilst the most frequently observed size was around 7 nm for E1GFF, no obvious diameter dominated in the case of E1GFFD. This could likely be the result

of (i) too few measurements and (ii) the propensity of these fibres to tightly bundle into combined fibres made of 2-3 sub-fibres, a phenomenon that can readily be observed by AFM and has been reported elsewhere.²⁵³ The smallest fibre size of 5 and 2 nm for E1GFF and E1GFFD respectively implies whilst the former might adopt a dimeric structure, as with E1FFF, the latter may assemble as a single molecule. Relating diameter distribution to the physical appearance of the gels, both E1GFF and E1GFFD gave cloudy gels implying a more heterogenous nanostructure with a range of aggregates whilst E1FFF transparent nature implied a well ordered, homogeneous nanostructure. The more Gaussian distribution of E1FFF as opposed to the evenly distributed histogram of E1GFFD is therefore in line with such observations by eye.

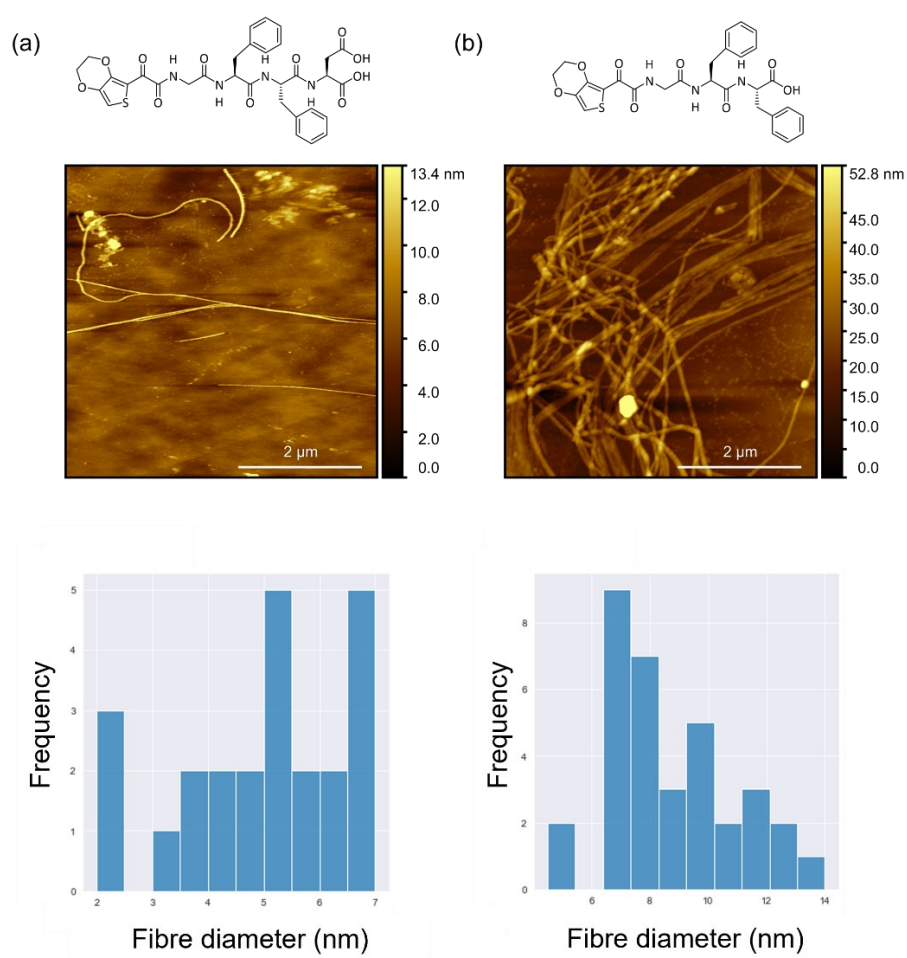


Figure 4-3. AFM images showing self-assembled fibres and corresponding histograms for (a) E1GFFD and (b) E1GFF

4.4.3 - Rheology of assembling systems

Rheology experiments were performed on the three gel-forming molecules, E1FFF, E1GFF and E1GFFD. The time-resolved sweep, shown in **Figure 4-4** below, monitored the change in storage (G') and loss (G'') modulus over a period of 12 hours after the addition of GdL to trigger gelation. Supplementary experiments (Appendix II - **Figure A 3**) demonstrated the choice of 1 Hz frequency and 0.1 % strain are well within the linear viscoelastic region whilst the frequency sweep indicates the rheological behaviour is frequency independent well above and below the chosen value of 1 Hz.

The first observation to make is that in all cases the storage modulus is greater than the loss modulus by at least an order of magnitude by the end of the 12-hour measurement period. Although rheological definitions of a hydrogel vary in the literature it is broadly agreed that at least around an order of magnitude difference should be observed to class the material as a gel.²⁵⁴²⁴⁸ All three of the molecules presented can therefore be said, at the concentration of 10 mM used, to form hydrogels. Secondly, it can be seen from the data below that the LMWG to form gels with greatest storage modulus is in fact E1GFF which reaches just over 36 kPa. Such a value is well within the storage modulus range in, for example, heart valve tissue.²⁵⁵ It might be tempting to compare this to the, albeit very rough, estimation of minimum gel concentration (MGC) from vial inversion tests of **Figure 4-1**. There it is E1FFF that shows the lowest MGC but of course the factors influencing lowest MGC are not necessarily those that determine greatest storage modulus at a given concentration. As such, a possible reason for the superior strength of E1GFF could be a result of its greater hydrophobicity when compared to E1GFFD yet greater flexibility when compared to E1FFF allowing for reorganisation and tighter, more strongly bound intermolecular packing. It could be speculated that E1FFF's greater hydrophobicity is likely what leads to it showing the lowest MGC as determined by a vial inversion test.

A final observation to be made is the shape of the respective curves. E1GFFD (**Figure 4-4c**) appears to show a more continuous evolution with no obvious sudden gradient changes that might suggest more than one regime in the micro-structure formation. The gradient does track in a rough sigmoidal pattern however and as such perhaps any morphological transformation are more gradual. E1FFF (**Figure 4-4a**) and E1GFF (**Figure 4-4b**) show distinct changes in gradient around 50 minutes and another around 150 and 300 minutes respectively. Such features might originate from structural transformations such as micelle-to-fibre or fibre-to-bundled fibre transitions.¹⁶⁹ It should be noted SAXS could potentially be employed to monitor the kinetics in evolution of the structures were further insight desired.

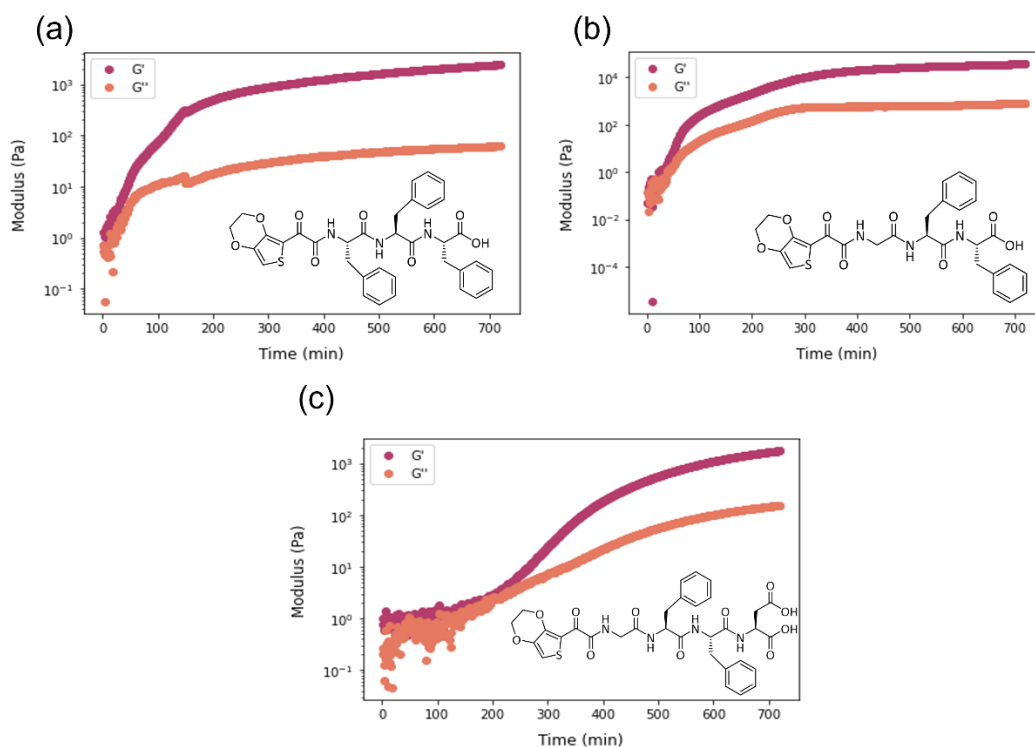


Figure 4-4. Shows the progression in storage (G') and loss (G'') modulus in the 12 hours following GdL addition for (a) E1FFF; (b) E1GFF and; (c) E1GFFD. All samples at 10 mM.

Monitoring the pH change throughout gelation can aid understanding of the structural evolution (**Figure 4-5**). In general, it seems all three gelators follow the same trajectory of decreasing pH beginning to buffer between a pH = 4-5 by around 3 hours. The buffering behaviour has been quantified to a first approximation in **Table 4-3** below. Whilst E1FFF and E1GFF seem relatively indistinguishable by this data, E1GFFD buffers at a noticeably higher pH of 4.8 suggesting an apparent pK_a of 7.6. This might seem counter-intuitive given the lower pH of isoelectric point (pI) for aspartic acid (pI = 2.77) vs phenylalanine (pI = 5.48).²⁵⁶ However, the pK_a of the aspartic acid side chain carboxyl being 3.65 to phenylalanines 1.83 C-terminus implies this periphery group will protonate significantly earlier as the pH drops.

Table 4-3. Table of the aggregate apparent pK_a of the compounds along with isoelectric points and pK_a of the amino acids found on the C-termini. pK_a and pI values taken from²⁵⁶

Compound	Apparent pK_a	C-terminus pI	C-terminus pK_a
E1FFF	6.80	5.48	1.83
E1GFF	6.60	5.48	1.83
E1GFFD	7.60	2.77	1.88, 3.65

Comparing E1FFF and E1GFF to their rheology data (**Figure 4-4a and b**) relative plateaus are reached around 200 minutes, when the pH buffers indicating the formation of a now more slowly evolving microstructure. Given the extensive body of literature in the area, approximately 200 minutes is likely the end of a transition to an entangled fibre like morphology that can now be rheologically categorised as hydrogels.¹⁶⁹ Interestingly, although E1GFFD also buffers around 200 minutes, albeit at a higher pH, the moduli do not plateau so obviously with a more continuous evolution of stiffness and later formation of a gel (10x difference seen by 400 minutes).

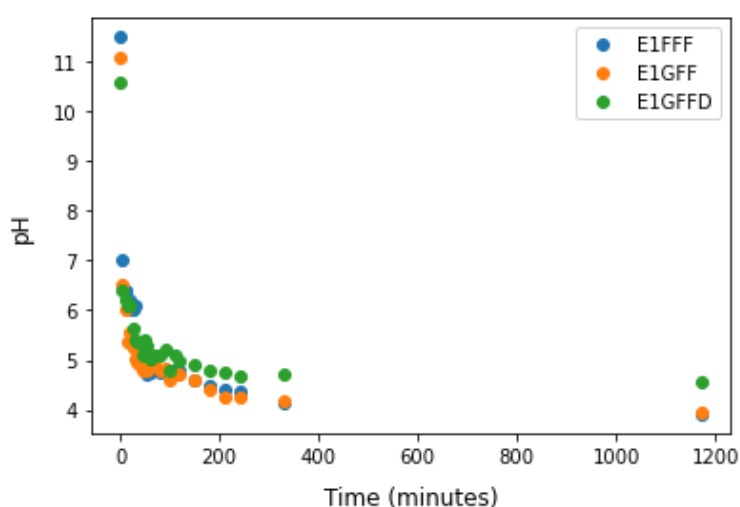


Figure 4-5. pH evolution over time throughout gelation of the three gel-forming compounds.

To add further insight into the assembly process, AFM images were taken throughout gelation (**Figure 4-6**). Before analysis is attempted it should be noted the samples were not diluted before preparation to preserve any structural features that might be concentration dependent. The danger of this is the tendency for the morphologies to often appear as large random aggregates that cannot be imaged through AFM and as such care had to be taken in interpreting the micrographs. Taking these images with the previous data can be interpreted in the following way.

E1FFF (**Figure 4-6a**) appears to show a fibre like morphology even before the GdL pH trigger is added. The main morphological change that was observed is a gradual transition from a loose to bundled fibre morphology. This can be observed by 2 hours where the pH has begun to stabilise at around pH = 4.8 and the shear modulus starts to plateau. Unlike the other gelators, it appears the presence of 3 phenylalanines preferentially encourages 1D fibre assembly even at high pH, perhaps through the

extensive hydrophobic effect and potential pi-pi interactions present in the molecule. The slow increase and decrease of storage modulus and pH respectively suggest a continuing evolution of the system likely due to further fibre bundling with incremental pH lowering.

E1GFF displays a distinctly different morphological evolution (**Figure 4-6b**). Here the nanostructure begins as spherical particulates that are gradually seen fusing together in a way reminiscent of the spherical to worm-like micelle transition described by the Adams group among others.¹⁶⁹ Whilst the apparent pK_a of the aggregates suggested by the buffering pH is similar to E1FFF it seems the presence of a glycine unit prefers spherical micelle assembly at higher pH values. This could be a result of increased flexibility and potentially reduced pi-pi interactions (though note debate exists as to accuracy of pi-pi stacking²⁵⁷) relative to E1FFF that allow assembly into a curved surface such as a spherical micelle. By 2 hours the system begins to show a tightly bundled fibre morphology however the shear modulus continues to evolve for the following hours suggesting a possible tightening and further bundling of the fibre morphology.

E1GFFD proved particularly challenging to image with film-like morphologies being consistently seen (**Figure 4-6c**). In general, though a shift from a particulate system to a bundled fibre system was also seen likely following a similar micelle to worm-like micelle to fibre bundle pathway to E1GFF. The flexibility of the glycine might allow this similarity however the presence of two acids that might be sequentially protonated on the C-terminus appears, certainly rheologically, to slow the transition somewhat.

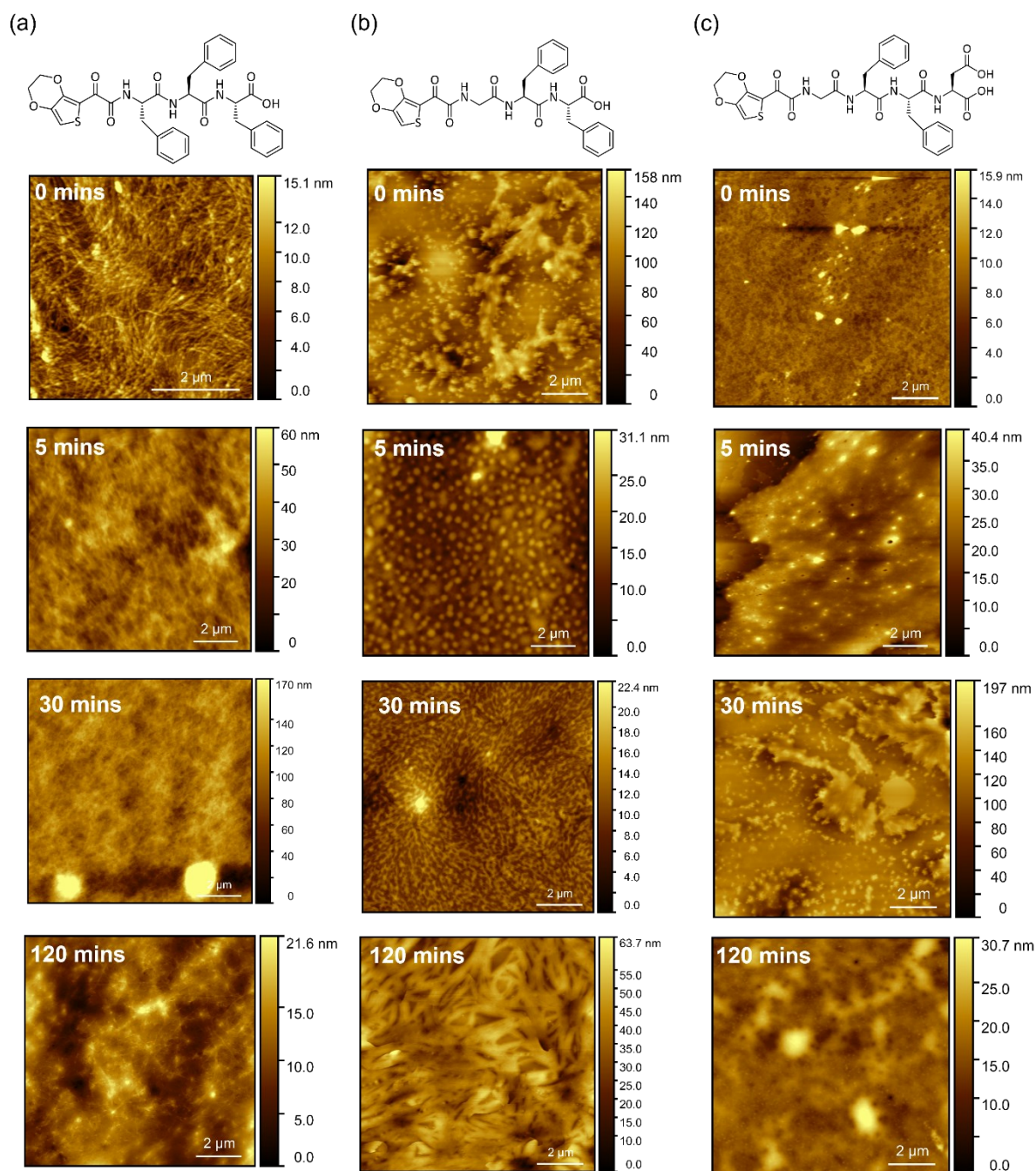


Figure 4-6. AFM images demonstrating the evolution in nanostructure of (a) E1FFF; (b) E1GFF and (c) E1GFFD as a function of time after GdL addition.

4.4.4 - Small angle X-ray scattering

Although indicative of the bulk morphology, AFM images still lack direct observation of the general structure in solution. To better understand the nature of self-assembled systems, bulk analysis techniques such as small angle X-ray and neutron scattering (SAXS and SANS respectively) are of

particular utility. SAXS is a technique that measures the scattering of X-rays from small angles typically between 0.1 and 5°. Using Bragg's law it can be inferred that the smaller the angle the bigger the structure that is probed and as such whilst conventional wide-angle X-ray scattering (WAXS) gives crystal structure information, SAXS allows for structural characterisation on the 1-100 nm length scale.²⁵⁸ By comparison with predicted scattering from basic models (tubes, spheres etc.), detailed analysis of nano-morphology can be obtained of the bulk sample, avoiding the compromising factors such as drying effects in AFM. As such, small angle scattering measurements has been used to great effect in describing the nanostructures present for LMWG systems.²⁵⁹

Using fitting software, basic models can be fit to the scattering data to extract parameters of the system such as fibre thickness, length etc. SAXS data was collected for the E1FFF gelator both before and after gelation. The data before (not shown) could not be fit to any specific model, implying a heterogenous system. This was curious given the observation by AFM of a fibre-like morphology before addition of GdL and could perhaps imply a heterogenous system, an AFM drying effect or be a result of insufficient data collection time. After gelation, however, a hollow cylinder model was shown to accurately fit the scattering data acquired (**Figure 4-7**). From this it could be inferred that the system appears to exist as hollow nanofibers with an internal radius of $6.36 \pm 0.21 \text{ \AA}$, wall thickness of $6.43 \pm 0.33 \text{ \AA}$ and average fibre length of $78.74 \pm 4.33 \text{ \AA}$ giving a total cross section of around 2.5 nm. Comparing this to the AFM diameters which found an average of ~5 nm shows some discrepancy. This may originate from measurement error or could be that two or more fibres bundled together tightly and was viewed as just a single feature when assessing the height profiles.

Certainly, the SAXS data shows beyond reasonable doubt the ordered nano-fibre assembly of the E1FFF in solution. Regrettably, data was not collected for the other gelators as these had not been investigated at the time of access to the equipment.

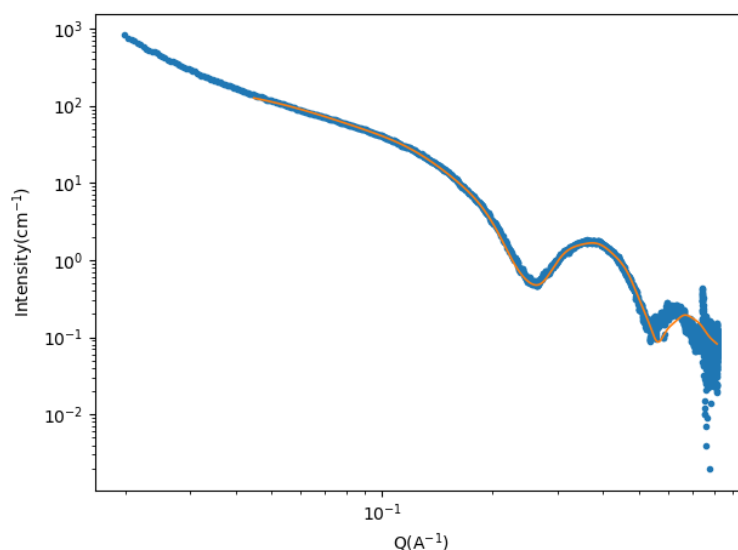


Figure 4-7. Small angle X-ray scattering (SAXS) data collected for E1FFF after gelation, blue circles are data obtained and yellow line shows the fit as obtained in SasView.

4.4.5 - Optoelectronic characterisation

UV-visible absorption spectroscopy can be a useful technique to interrogate several aspects of the assembly in LMWG systems. Dilution series are particularly useful as they allow potential observation of transitions from macro-assembled to oligomeric to even dimeric/monomeric species as the samples are diluted. These were therefore performed on the three gelators (**Figure 4-9**). The first observations to be made are of any peak maxima shifting as a function of concentration.

In Kasha theory of molecular aggregates, dimeric species will produce two delocalised states composed of either the in phase or out of phase contributions from the local excited states of the respective molecules. When both molecules exist side-by-side, known as H-aggregation, the in-phase state is preferred leading to an enhanced dimeric dipole relative to the monomer. Conversely when stacked head-to-tail as determined by the magic angle, θ_M , (**Figure 4-8**) known as J-aggregation, the in-phase is forbidden and the out of phase transition instead dominates. It is thought that shifts in the peak values in the UV-visible absorption for supramolecular systems such as ours may be indicative of at least H- or J-like aggregation.²⁶⁰

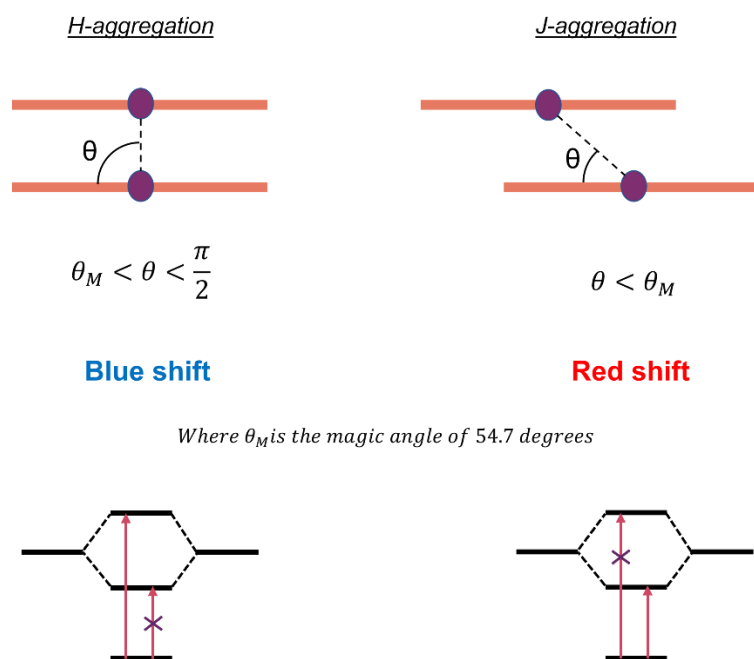


Figure 4-8. Schematic depicting the phenomena of H- and J-aggregation as described by Kasha theory. As the angle between the two dipoles is increased beyond θ_M , transitions from the ground state to the lower of the two possible states is preferred to the higher and visa versa. This is a result of the changing orientation bringing the dipole moments of the lower energy transition into phase that of higher energy out of phase.²⁶⁰

The slight but significant red shift observed here in E1GFFD (**Figure 4-9a**) could therefore suggest J-like aggregation implying a slightly staggered stacking arrangement. It is possible that the increased area of coulombic repulsion from the aspartic acid C-terminus causes a slight offset in successive molecules to be required in stacking. Looking at the data from E1FFF however (**Figure 4-9c**), a substantial blue shift can be seen suggesting H-like aggregation and an aligned stacking arrangement. Possible intuition for this behaviour could come from the greater density of pi stacking sites present in E1FFF that preferentially organise molecules directly above and below one another enforcing 1-dimensional assembly.

Interestingly, no discernible shift was seen for E1GFF, implying possibly insufficient dipole coupling. Adjacent EDOT moieties may be staggered too far from one another or a mixture of H and J like aggregation may be present. Normalisation of the data to investigate peak broadening revealed no significant difference between the highest and lowest concentration, although changes in peak width are seen approaching the concentration at which a switch from 1 mm to 10 mm pathlength cuvette was undertaken (2.226 mM – necessary for probing a wide concentration range), demonstrating how reaching the limit of detection at 1 mm can obfuscate the measurement through noise.

Though useful, it should be noted his model is highly idealised and was made to describe discrete dimers. Further, it has been noted since its inception that Kasha theory neglects the finer vibronic structure of molecules as well as restricting itself only to coulombic coupling, ignoring quantum mechanical contributions from, for example, wavefunction overlap.^{261 260} Therefore, its use in large, supramolecular aggregates should be done so tentatively with it only implicating H- or J-like aggregation.

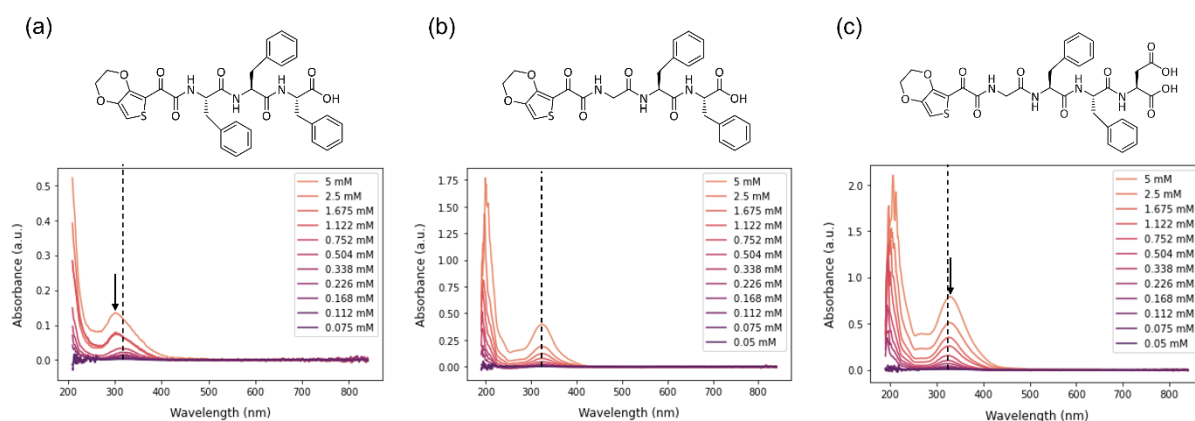


Figure 4-9. UV-visible absorption profiles from 0.5-5 mM of E1GFFD (a); E1GFF (b) and: E1FFF (c)

As mentioned, the data can be further analysed to pick up changes in extinction coefficient (ϵ) with concentration. Comparison of this with ϵ of the monomer in solution can give an idea of the emergence and competition of various aggregated species since complexes such as oligomers or larger structures will typically absorb less than their monomeric counterpart. This has been graphically represented in **Figure 4-10**. Though the data is somewhat noisy, a possible artefact of the detection limit and cuvette sizes used, several comments can be made.

It can generally be assumed that gelator molecules dissolved in DMSO exist completely solvated and therefore monomeric. Comparing the ϵ of the DMSO dilution data, negligible differences can be seen between the samples. This is as expected since ϵ is here derived from the EDOT region (290-400 nm) of absorption. In all cases the DMSO ϵ values are significantly greater than any obtained in aqueous dispersions/gels. This is anticipated since the molecules are thought to be free in solution and therefore devoid of any aggregation-induced scattering and shielding from the incident light that might lessen the absorption.

Comparing the changing ϵ before and after gelation it can be seen in general the samples showed no indication of trending towards the monomeric species. This further indicates dilution of the gelators

might move them between structural types (e.g. entangled to free fibres or fibres to spherical micelles) but not toward monomeric species. Whatever structure(s) dominate upon dilution, they appear stable at low concentrations over free monomers in solution in all cases, an observation that should perhaps be unsurprising given the hydrophobic and highly aromatic nature of the molecules chosen.

Comparing pre- and post-gelation, both E1GFF and E1GFFD exhibit little evidence of convergence indicating distinctly different assembled species are preserved across the dilution range before and after the pH-triggered assembly. Given previous AFM images, these are expected to be tightly bundled fibre morphologies. The more uniform spread in fibre diameter distributions seen (**Figure A 2**), particularly for E1GFFD, implies these systems preferentially bundle even to low concentrations perhaps preventing any detectable change in phase through dilution. In the case of E1FFF however there appears to be a convergence of the two aqueous based measurements. This is consistent with observation of fibres at pre-gelation in AFM (**Figure 4-6a**), it seems likely that dilution transitions the gelled system from a bundled to loose fibre state to meet the ϵ of the pre-gelled sample, a result that is unsurprising given literature precedent.¹⁶⁹

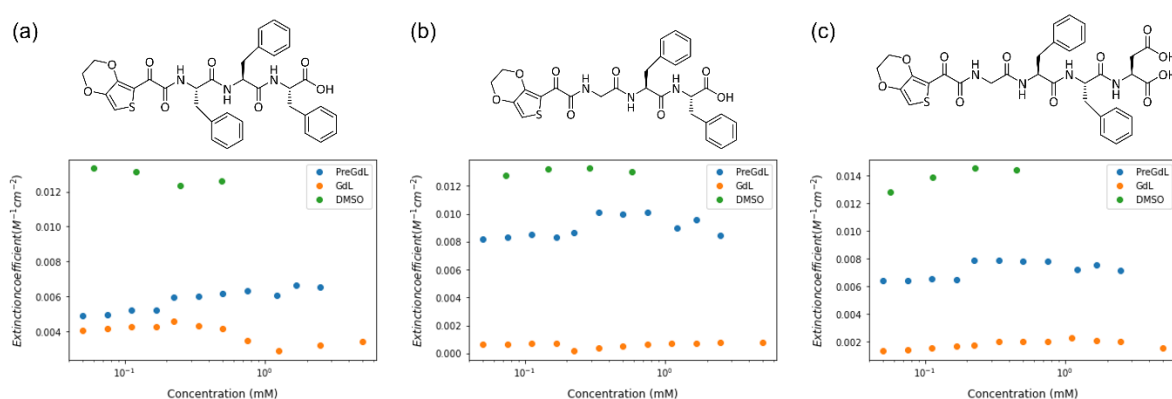


Figure 4-10. Illustration of the changing extinction coefficient for the three gelators in the high pH, mixtures before addition of GdL, after addition of GdL and gelation (> 12 hours) and in DMSO for (a) E1FFF; (b) E1GFF and; (c) E1GFFD respectively. Variation in peak wavelength with concentration meant peak choice was simply that which was most common across the dilution, this was at 324, 325 and 325 nm for E1FFF, E1GFF and E1GFFD respectively.

4.4.6 - Techniques omitted

A common workflow for LMWG systems would include techniques such as circular dichroism (CD) and Fourier-transformed infra-red spectroscopy (FT-IR). Although some data was collected for both these

techniques it was not included as was deemed to not add to the investigation. FT-IR has typically been employed to identify hydrogen bonding and relate this to any secondary structure such as α -helices or β -sheets. Given the dominating stretches from water that would drown out H-bonding information samples are usually analysed in deuterated solvents that run the risk of providing different structures to their hydrogenated counterparts.¹⁶⁹ Moreover, interpretation can be difficult with literature examples of the sample peptide system suggesting completely different secondary structures.^{262,263}

Ostensibly, CD is used to build a picture of chirality in the system and possible rotations in the propagating fibres. Obtaining useful data however is often fraught with problems such as scattering artefacts and the strong absorption of aromatics that can obfuscate information about the peptide packing. Use of thinner cuvettes and more diluted solutions can be performed but run the considerable risk of forcibly aligning the gel fibres and changing the structure respectively.¹⁶⁹ Again, different data have been reported separately for the same molecule.^{263–265} Very little could be learned from the data collected for mono-EDOT-peptide systems and so it is not included.

Finally, since the aim of this work is ultimately to create materials capable of charge transport some conductivity characterisation was carried out, mainly in the form of impedance spectroscopy. However, whilst ionic conductivity will always be observed in such aqueous systems, the electronic component for a monomer is negligible and interpretation of the data, which will require comparison between wet and dry samples with four-point probe measurements, is ongoing to extract a meaningful electronic contribution. With the aid of small-angle neutron scattering (SANS) experiments, a rationalised circuit fitting model will be proposed to properly interrogate the charge transport observed.

It is anticipated that the presence of just one EDOT unit in the examples displayed here will limit the electronic charge transport potential. Therefore, as will be discussed in the future work section, longer EDOT oligomer have already been synthesised incorporating these peptide sequences both dimeric and trimeric that are hoped to provide hydrogels with significant electronic conduction.

4.5 - Conclusions and future work

Herein the design, preparation and characterisation of EDOT-based supramolecular gelators have been described for, to the best of our knowledge, the first time. It has been shown modulation of the peptide sequence can substantially alter the assembly pathway either toward or away from a spherical micelle starting point appearing to depend on the degree of hydrophobicity. The EDOT-peptides were

able to exhibit storage moduli up to 36 kPa, a value that could be tuned by modifications in the peptide sequence. The presence of glycine as a point of flexibility seemed to be key in not only dictating the mode of assembly but also the mechanical properties with the possibility of increased moduli with tighter molecular packing. Such hydrogels may have utility in biomedical applications however it is anticipated their oligomeric counterparts be even more so.

The design rules explored here will be extended to longer EDOT oligomers. Work is already in progress with the successful synthesis of dimeric and trimeric species. The investigation of their assembly is already underway with fibre formation observed, and it is anticipated that they will exhibit charge transport to a suitable level for a viable conductive biomaterial. Simultaneously, cell viability studies will be conducted to ascertain their suitability in an *in vivo* context. The charge transport properties, though already being investigated, will be elucidated through the combined use of impedance spectroscopy as well as dry and wet four-point probe measurements in order to extract meaningful charge transport quantities.

4.6 - Experimental

All details not included here regarding material and characterisation can be found in the general experimental section of Appendix I.

4.6.1 - General peptides synthesis protocol

Latterly in the project, a Biotage Initiator Alstra+ was used to make all but E1FFD as it gave greater coupling efficiencies. The protocol for synthesis 'by hand' is reported below and was used to synthesise E1FFF, E1FFD and E1FF early on in the research.

Peptides were constructed using a conventional solid-phase technique and capped at the N-terminus with the requisite EDOT oligomer. In brief the resin was swelled in DCM inside a capped and fritted syringe. This was expelled and replaced with a solution of the amino acid (3 eq) and N,N-diisopropylethylamine (DIPEA) (6 eq) the estimated amount of available chlorotriyl chloride on the resin being designated as 1 eq. This was shaken overnight after which the mixture was expelled, the resin washed 5x with DCM, 5x with DMF followed by shaking with 3 mL of a 9:1:0.5 DCM:MeOH:DIPEA solution for 20 minutes. If the peptide synthesiser was used this was the point at which they would be loaded after a further 5x DCM, 5x DMF wash. Samples would need only be cleaved after automated

synthesis (see cleavage protocol below). To cleave Fmoc groups on the N-terminus the mixture was expelled, the resin again washed 5x with DCM and DMF respectively and then shaken with 3 mL 20% piperidine in DMF for 1 minute. This was expelled and replaced again with 3 mL 20% piperidine for 20 minutes. To couple amino acids to the free amine the resin was again washed 5x with DCM and DMF respectively following which a 2-3 mL solution in dry DMF of the amino acid (3 eq), DIPEA (6 eq) and HATU (0.95 eq) was taken up and shaken for between 30-60 minutes. The above cleavage and coupling procedures were repeated as many times as necessary to build the required peptide. Between each step a Kaiser test was performed to check for coupling and cleavage success. When coupling the final EDOT-COOH capping group the same procedure was used as described above only often with < 3 eq depending on availability.

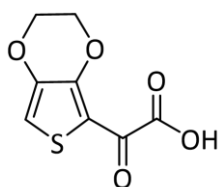
To cleave the EDOT-peptides from the resin 3 mL of 20% trifluoroacetic acid (TFA) in DCM was taken up and shaken for 15-20 minutes. The solution was transferred into a round-bottom flask (RBF) and concentrated on a rotary evaporator with the assistance of more DCM as an azeotrope if needed.

4.6.1.1 - High Performance Liquid Chromatography (HPLC) Purification

HPLC purification was performed on a Shimadzu FRC-10A with a typical flow rate of 10 ml/min. In a typical purification the OEDOT-peptide was dissolved in H₂O/MeCN by first adding 20 mL H₂O and then slowly adding up to 20 mL of MeCN until dissolved. Most of the time this required close to a 1:1 mixture for full dissolution. This was then filtered through a 0.45 µm Teflon filter and applied to the column with a starting H₂O/MeCN concentration to match that in which dissolution occurred. Typically, the H₂O/MeCN gradient would be as follows: Isocratic at 50% MeCN for 10 minutes, increase to 95% over 10 minutes, hold at 95% for 5 minutes, return to 50% for 5 minutes. Collected fractions would be dried of MeCN on a rotary evaporator then freeze dried to yield the final product with high purity.

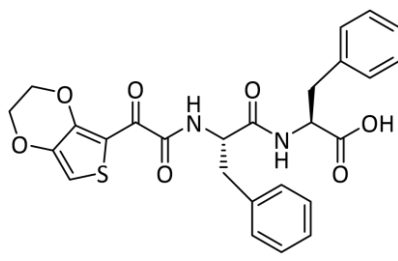
4.6.2 - Synthesis

EDOT-COOH (2 steps): 2-(2,3-dihydrothieno[3,4-b][1,4]dioxin-5-yl)-2-oxoacetic acid



Oxalyl chloride (2.55 ml, 30 mmol, 1 eq) was added in a drop-wise fashion to a solution of EDOT (3.15 ml, 30 mmol, 1 eq) in dioxane. The solution was heated to 100 °C for 1 hour stirring constantly. Once cooled to room temperature, methanol (90 ml) was added along with triethylamine (5 eq) following which the mixture was stirred for a further 3 hours. Excess alcohol was then removed *in vacuo*. The mixture was then diluted with DCM, washed with water and brine, the separated organic layers dried over MgSO₄, filtered and concentrated *in vacuo*. The resulting residue was then purified by column chromatography using 50 % EtOAc in Hexane to yield the desired methyl ester as a yellow solid. This ester was then dissolved in THF (100 ml), an excess of 1M NaOH (> 5 eq) aqueous solution added and the solution stirred for 2 hours. Excess THF was evaporated off following which the mixture was acidified with 1M HCl (100 ml) the precipitate was centrifuged and washed with DI water (3 x 100 ml). The solid was dried by lyophilisation yielding the desired oxalyl acid in a 64% yield over 2 steps. Spectroscopic data was consistent with those reported previously.¹⁹⁴ ¹H NMR (400 MHz, CDCl₃): δ = 7.35 (1H, s, -S-CH), 4.38 (2H, m, -O-CH₂-), 4.27 (2H, m, -O-CH₂-)

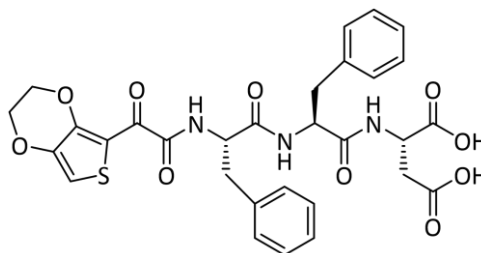
E1FF: (2-(2,3-dihydrothieno[3,4-b][1,4]dioxin-5-yl)-2-oxoacetyl)-L-phenylalanyl-L-phenylalanine



¹H NMR (400 MHz, d₆-DMSO): δ = 8.46 (1H, d, NH, J = 8.7 Hz), 8.25 (1H, d, NH, J = 8.0 Hz), 7.23 – 7.10 (10H, m, phenyl ring protons), 4.61 – 4.53 (1H, m, NH-CH), 4.49 – 4.43 (1H, m, NH-CH), 4.25 – 4.22 (2H, m, EDOT -O-CH₂), 4.20 – 4.16 (2H, m, EDOT -O-CH₂), 3.09 – 2.73 (4H, m, CH₂-Ph) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 177.05, 172.97, 170.50, 162.49, 150.04, 141.96, 137.89, 137.82, 129.68, 128.68,

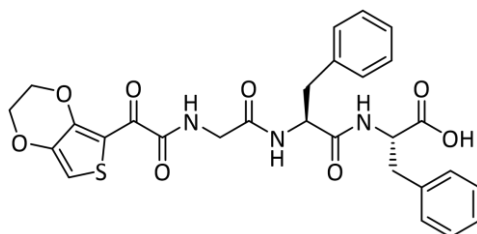
128.56, 126.95, 126.85, 114.55, 111.22, 65.76, 64.27, 54.33, 54.05, 37.71, 37.40, 29.56. LRMS m/z ESI+: Calc: 508.13 Found: 509.0 $[M+H]^+$, 531.0 $[M+Na]^+$.

E1FFD: (2-(2,3-dihydrothieno[3,4-b][1,4]dioxin-5-yl)-2-oxoacetyl)-L-phenylalanyl-L-phenylalanyl-L-aspartic acid



^1H NMR (400 MHz, d_6 -DMSO): δ = 8.59 (1H, d, NH , J = 8.8 Hz), 8.49 (1H, d, NH , J = 7.9 Hz), 8.33 (1H, d, NH , J = 8.5 Hz), 7.31 – 7.13 (10H, br, PhH), 4.62 (1H, sextuplet, NH-CH , J = 4.6 Hz), 4.59 – 4.52 (2H, m, NH-CH), 4.29 – 4.27 (2H, m, $-\text{O-CH}_2$), 4.23 – 4.20 (2H, m, $-\text{O-CH}_2$), 3.10 – 2.77 (4H, m, Ph-CH_2), 2.76 – 2.58 (2H, m, CO-CH_2) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 206.76, 177.09, 170.42, 162.46, 150.01, 141.95, 138.21, 137.90, 129.77, 128.53, 126.80, 114.51, 111.25, 65.75, 64.27, 54.59, 54.35, 38.00, 37.74 ppm. LRMS m/z ESI+: Calc: 623.16

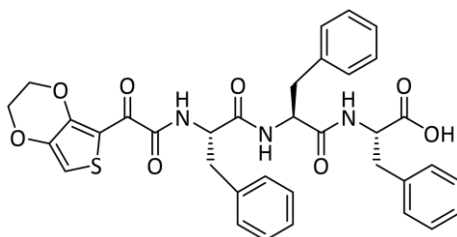
E1GFF: (S)-N-((S)-5-(2-(2,3-dihydrothieno[3,4-b][1,4]dioxin-5-yl)-2-oxoacetamido)-3,4-dioxo-1-phenylpentan-2-yl)-2-(hydroxyamino)-3-phenylpropanamide



^1H NMR (400 MHz, d_6 -DMSO): δ = 8.74 (1H, t, NH (glycine), J = 6.0 Hz), 8.37 (1H, d, NH , J = 7.8 Hz), 8.07 (1H, d, NH , J = 8.5 Hz), 7.29-7.02 (10H, m, phenyl ring protons), 4.56 (1H, td, NH-CH , J = 9.0, 4.3 Hz), 4.43 (1H, m, NH-CH , J = 8.4, 5.4 Hz), 4.38-4.31 (2H, m, EDOT $-\text{O-CH}_2$), 4.27-4.20 (2H, m, EDOT $-\text{O-}$

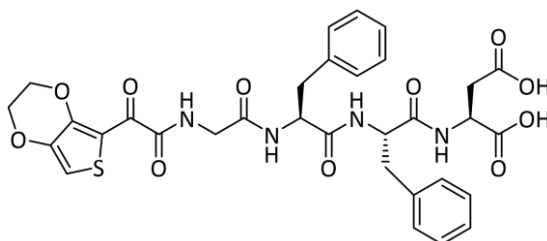
CH₂) 3.82-3.62 (2H, m, NH-CH₂), 3.11-2.68 (4H, m, CH₂-Ph) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 192.03, 162.91, 155.78, 152.22, 150.08, 129.75, 129.63, 128.68, 128.49, 114.61, 65.63, 64.44, 53.99. LCMS *m/z* (ESI+) Calc: 565.2; Found: 566.1 (M+H), 588.0 [M+Na]⁺

E1FFF: (S)-N-((2S,5S)-5-(2-(2,3-dihydrothieno[3,4-b][1,4]dioxin-5-yl)-2-oxoacetamido)-3,4-dioxo-1,6-diphenylhexan-2-yl)-2-(hydroxyamino)-3-phenylpropanamide



¹H NMR (400 MHz, d₆-DMSO): δ = 8.61 (1H, d, NH, J = 8.9 Hz), 8.38 (1H, d, NH, J = 7.8 Hz), 8.26 (1H, d, NH, J = 8.5 Hz) 7.32-7.08 (15H, m, PhH), 4.60 (1H, td, NH-CH₂, J = 9.0, 4.5 Hz), 4.55-4.44 (2H, m, NH-CH₂, presumed two td overlapping, J values not clear), 4.33-4.15 (4H, m, O-CH₂), 3.11-2.73 (6H, m, NH-CH-CH₂) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 176.47, 173.45, 170.43, 162.24, 149.92, 141.74, 138.16, 129.82, 129.64, 128.74, 128.53, 126.80, 115.19, 110.97, 65.98, 64.16, 54.22. LRMS *m/z* ESI+: Calc: 655.20 Found: 656.0 [M+H]⁺, 678.3 [M+Na]⁺

E1GFFD: (S)-4-(((S)-1-(((S)-5-(2-(2,3-dihydrothieno[3,4-b][1,4]dioxin-5-yl)-2-oxoacetamido)-3,4-dioxo-1-phenylpentan-2-yl)amino)-1-oxo-3-phenylpropan-2-yl)amino)-3-(hydroxyamino)-4-oxobutanoic acid



¹H NMR (400 MHz, d₆-DMSO): δ = 8.74 (1H, t, NH (glycine), J = 6.1 Hz), 8.33 (1H, d, NH, J = 7.9 Hz), 8.23 (1H, d, NH, J = 8.4 Hz), 8.04 (1H, d, NH, J = 8.4 Hz), 7.32 – 7.07 (10H, m, phenyl ring protons), 4.59 – 4.48 (3H, m, NH-CH₂), 4.37 – 4.32 (2H, m, EDOT -O-CH₂), 4.26 – 4.21 (2H, m, EDOT -O-CH₂), 3.81 – 3.63 (2H, m, NH-CH₂), 3.11 – 2.55 (6H, m, CH₂-COOH and CH₂-Ph) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 207.06, 172.48, 171.85, 171.17, 167.96, 162.51, 150.48, 138.12, 129.82, 129.76, 128.58, 128.49,

126.80, 114.90, 65.47, 64.23, 38.05, 31.22 ppm. LRMS m/z ESI+: Calc: 680.18; Found: 680.7 $[M+H]^+$, 703.0 $[M+Na]^+$

4.6.3 - General assembly protocol

The assembly experiment was based on a technique pioneered by the group of Dave Adams.²⁶⁶ In a typical experiment the OEDOT-peptide was sonicated in MQ water with 1.5 eq NaOH until dissolved. Typically, this would be at a concentration of around 7-12 mM. To this was added 2 eq of glucono- δ -lactone (GDL) in MQ water and left on the benchtop overnight to allow for the slow hydrolysis of the GDL and subsequent gradual pH drop.

4.6.4 - Characterisation

4.6.4.1 - Atomic force microscopy (AFM)

Measurements were performed on a 5500 Agilent AFM using an AC240TS-R3 cantilever from Oxford Instruments ($f = 70$ kHz, $k = 2$ N/m, no tip coating) with AC tapping mode in air. Typically, substrates were prepared on Si by diluting down to 0.1 mM then applying 5-10 μ l to the surface for 10-20 minutes following which a Kimwipe was used to wick off remaining liquid. Samples were imaged within 48 hours of preparation.

4.6.4.2 - Rheology

Rheology measurements were taken using an Anton Paar MCR 302 Modular Compact Rheometer. Samples were measured using a 25 mm plate. Time sweeps were conducted at 1 Hz, strain of 0.1% and at steady state with max equilibration time of 200 seconds. A data point was collected every minute for 12 hours. To justify the frequency and strain values used a frequency sweep ($f = \log$ sweep 100 – 0.01 Hz, strain – 0.1%, steady state with max equilibration time = 200s, 10 data points per decade) and strain sweep ($f = 1$ Hz, strain log sweep 0.01-100 %, steady state with equilibration time = 20 s) were conducted. It was observed that the gels displayed stable storage and loss modulus behaviour in the values chosen for the time sweep.

4.6.4.3 - pH profiling

A Mettler Toledo fiveeasy plus pH meter was used. The equipment was calibrated to 4, 7 and 10 pH standards before use. The probe tip was rinsed thoroughly with DI water between each measurement and the probe held in the gelling solutions for at least 30 seconds to stabilise the value. pKa calculations were inferred using a concentration of 10 mM and the following equation.

$$pKa = -\log_{10} \left\{ \frac{[H^+]^2}{[HA] - [H^+]} \right\} = -\log_{10} \left\{ \frac{(1/10^{pH})^2}{([HA] - (1/10^{pH}))} \right\}$$

Where $[H^+]$ is the concentration of protons dissociated and $[HA]$ is the concentration of the molecule in question.

4.6.4.4 - Small angle X-ray scattering (SAXS)

Measurements were taken on a benchtop SAXS setup in the Tokyo Institute of Technology. An X-ray source of 1.5405 Å was used and backgrounds taken using just MilliQ water.

Chapter 5 - Controlled fractal assembly of semiconducting polymers

5.1 - Introduction

So far, the assembly of *oligo*-EDOT based systems has been demonstrated in nanofibrous, hydrogel form, but what potential do semiconducting *polymer* systems have to self-organise? Are there perhaps more exotic nanostructures that might be realised and utilised? With the nano-morphological properties of semiconducting devices being consistently shown to drastically effect device performance,^{267–269} understanding and control of this length scale could allow for optimisation of the potential from such systems (organic photovoltaics, organic light emitting diodes etc.). Furthermore, the complex and often dendritic nature of charge transporting tissue such as neurons may integrate better with more intricate semi/conductive biomaterial morphologies.

In this work we demonstrate the ability of brush co-polymers based on the semiconducting polymer 9-dioctylfluorene-alt-benzothiadiazole, commonly known as F8BT, to self-assemble into interconnected fractal patterns when conjugated with polyethylene glycol (PEG) chains of sufficient length. With the assistance of simulations, we provide a possible explanation for this behaviour that considers an interplay of solvation and inter-particular PEG chain entanglement as well as providing small angle neutron scattering (SANS) data to suggest that assembly occurs in solution.

5.2 - Background

Fractals can be defined as patterns that persist in matter when magnification is varied repeating at ever smaller or larger scales of length.²⁷⁰ Such patterns are ubiquitous in nature across an enormous range of length scales from the microns of snowflakes to the light years of galaxies. Despite this,

examples demonstrating controlled assembly of fractal patterns in human-made systems are scarce and often incidental. Those that do exist can be divided into two types, top-down and bottom-up fabrication. In top-down methods, a range of lithographic techniques have been utilised to achieve fractals, or fractal-like patterns on surfaces down to the nanometer scale.²⁷¹

Bottom-up approaches require fine control and understanding of building blocks to assemble into intricate fractal patterns. Molecular assembly has been demonstrated to form fractal patterns such as Sierpinski's triangle²⁷² and a hexagonal gasket.²⁷³ Protein and peptide building blocks have received particular interest in this vein through the specificity and directionality of, for instance, host-guest interactions. Intricate fractal assemblies have been demonstrated by protein/ligand inducing strategies,²⁷⁴ short peptide sequences²⁷⁵ and even DNA origami.²⁷⁶ One example of particular interest displayed the assembly of two homo-oligomeric proteins through appendage of Src homology 2 (SH2) domain or phosphorylatable SH2-binding peptides into dendritic, fractal structures. The authors conceived the design through atomistic modelling whereupon they went on to demonstrate its efficient capture and release of cargo proteins in response to phosphorylation.²⁷⁷

Whilst there are relatively few experimental examples of fractal formation, the modelling field has been able to simulate their formation for 40 years primarily through the diffusion limited aggregation (DLA) models first put forward by Witten and Sander.²⁷⁸ The model is relatively simple, yet capturing the resulting behaviour mathematically has been particularly challenging. In brief, spheres are allowed to move by Brownian motion and upon touching another sphere they bind together at the point of contact. From here complex dendritic, fractal patterns are readily generated. Another mode of fractal modelling is ballistic aggregation (BA). BA works similarly to DLA only the particles are now endowed with kinetic energy yielding often more compact fractal networks.²⁷⁹ Since their first inception these models have been elaborated on significantly to explore interaction radii,²⁷⁹ expanded into 3-dimensions²⁸⁰ and hybridised with other models such as strange attractors (SAs)²⁸¹ to name a few.

Examples involving semiconducting polymer systems are incredibly rare. The only instance found using a conjugated polymer system came from Tae Lim Choi's group where the block copolymer poly(*endo*-tricyclo[4.2.2.0]deca-3,9-diene)-*b*-poly(*p*-phenylenevinylene) (PTD-*b*-PPV) was shown to form fractal-like structures on the micron length scale in situ. Though remarkable, the constituent polymers exhibit unremarkable semiconducting properties and exist as a stand-alone example generating only small fractals.¹⁶⁷

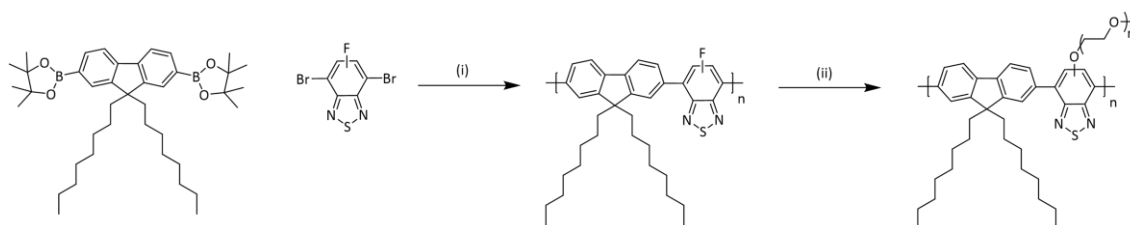
Herein we explore the capability of the highly ubiquitous semiconducting polymer poly(9,9-dioctylfluorene-*alt*-benzothiadiazole) (F8BT) grafted with poly(ethylene glycol) (PEG) side-chains as brush co-polymers to form large fractal structures covering 10s of microns. The mode of assembly is

interrogated using small angle neutron scattering (SANS), modification of PEG chain length, hydrophilic quantification and DLA-based simulations, as well as design rules postulated for generalising the phenomenon.

5.3 - Results and Discussion

5.3.1 - Synthesis

Production of the F8BT derivative follows work previously published by Creamer et al. that details its functionalisation through aromatic nucleophilic substitution.²⁸² In brief, a fluorinated derivative of F8BT is synthesised by copolymerising 4,7-dibromo-5-fluoro-2,1,3-benzothiadiazole and 9,9-dioctyl-9H-fluorene-2,7-diboronic acid bis(pinacol) under Suzuki conditions. The additional fluorine group can be leveraged to functionalise the polymer in a broad range of ways (**Scheme 5-1**). For this work, a hydroxyl terminated PEG chain was used as the attacking nucleophile and the degree of functionalisation characterised with NMR and UV-visible spectroscopies (through the relative heights of peak maxima around 325 and 430 nm).



Scheme 5-1. General synthetic scheme for fabrication of PEG-grafted F8BT. Conditions: (i) $\text{Pd}(\text{PPh}_3)_4$, Na_2CO_3 , Toluene, 120 °C; (ii) NaOH, PEG_n , DMF, CB, 120 °C, $n \approx 350$, $m = 8\text{-}110$.

In this work a total of four different PEG lengths were investigated: 0.75, 2, 5 and (later on) 10 kDa respectively deliberately encompassing a wide range of solubilities in water. The polymer system is visualised below in **Figure 5-1** as a brush copolymer architecture consisting of a hydrophobic backbone decorated by hydrophilic PEG chains.

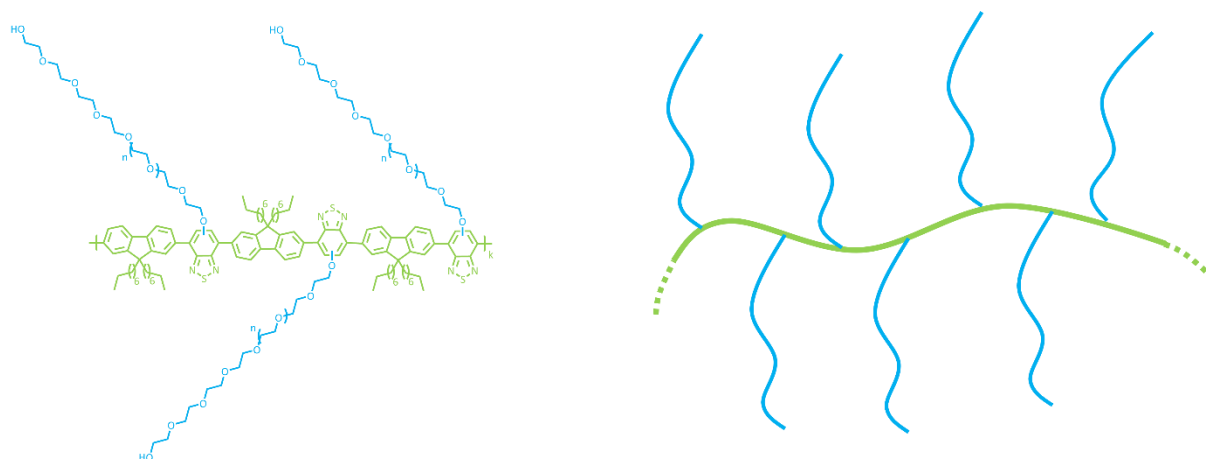


Figure 5-1. Schematic illustrating the structure of the brush copolymers

5.3.2 - Assembly conditions

Conditions that attempt to induce self-assembly were inspired by Wong et al.²⁸³ In this work the authors showed the self-assembly of block copolymers into polymersomes of different aspect ratio by controlling the slow evaporation of different THF proportions when mixed with water. We therefore elected to mix solutions of PEGylated F8BT, dissolved in THF, with varying proportions of water. This was followed by gentle stirring over the course of three days to allow the THF to evaporate (**Figure 5-2**).

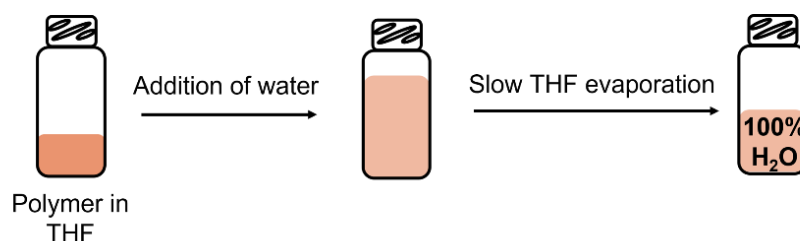


Figure 5-2. Schematic illustrating the assembly protocol undertaken

The conditions outlined in the table below were initial attempted, as such conditions had been reported for the assembly of polymersomes with differing aspect ratios.²⁸³

Table 4. Table outlining the conditions initially attempted

Initial concentration in THF (mg/ml)	Starting THF ratio	Starting H ₂ O ratio
0.5	1	1
0.5	3	1
0.5	5	1

Initial experiments were conducted only for 0.75 kDa, 2 kDa and 5 kDa PEG F8BT (hereafter referred to as 750PF, 2KPF and 5KPF respectively) samples at 0.5 mg/mL and with THF:Water ratios outlined above (**Table 4**). In these preliminary experiments the final concentrations would obviously vary as a function of the THF:Water ratio used, a factor that will be normalised in due course. After stirring for 3 days samples were all diluted to 0.1 mg/mL and spotted on silicon substrates for atomic force microscopy (AFM) imaging. Whilst the features seen in the 750PF and 2KPF proved unremarkable and seemingly disorganised (**Figure 5-3a** and **b**), samples prepared using 5KPF under the 1:1 condition yielded remarkable fractal-like aggregates (**Figure 5-3c**). Though intriguing these initial observations were feared to be an unreproducible oddity. Subsequent repeats of the experiment however again showed fractal-like structures for the same conditions.

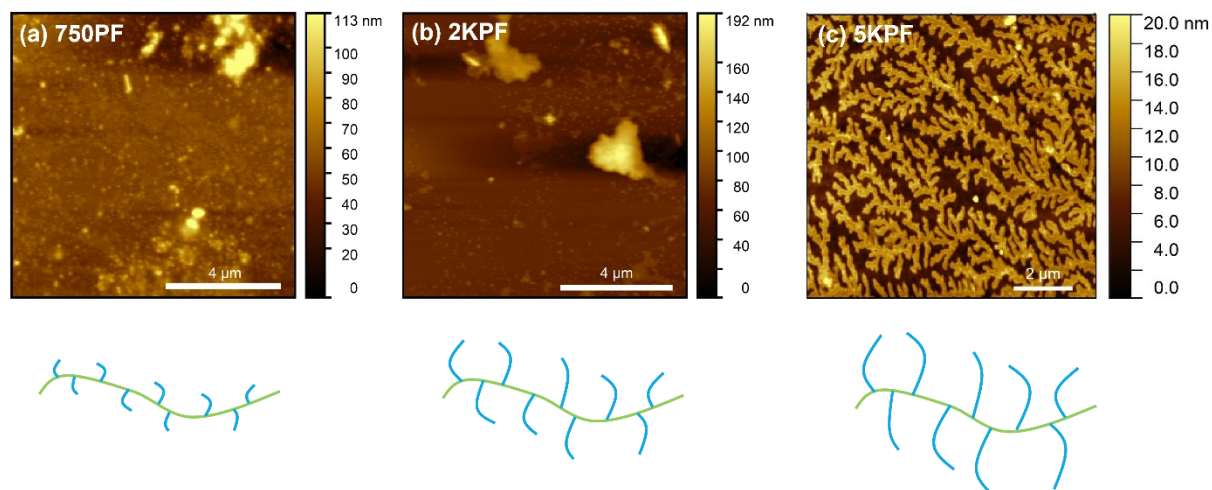


Figure 5-3. Atomic force microscopy (AFM) images of (a) 750PK; (b) 2KPF; and (c) 5KPF all prepared using a 1:1 THF:H₂O assembly ratio. Below each is a schematic representation of the brush copolymer with increasing PEG chain length, a critical point appears to be reached between 2KPF and 5KPF allowing fractal formation.

As shown in **Figure 5-4**, variation in the THF:H₂O ratio for assembly yielded more clustered and globular structures when higher proportions of THF were used. Since at the moment of sample deposition to the silicon substrate, all sample were diluted to 0.1 mg/mL regardless of previous

conditions it was encouraging to see distinct differences by AFM as it indicated the assembly conditions were responsible. It was speculated the increased gradient of solvent change and higher final concentration might cause the polymers to cluster more, forming the non-fractal, globular aggregates observed. However, at this point it was not possible to rule out that the fractal morphologies were a result of drying onto the silicon substrates and not in-solution assembly.

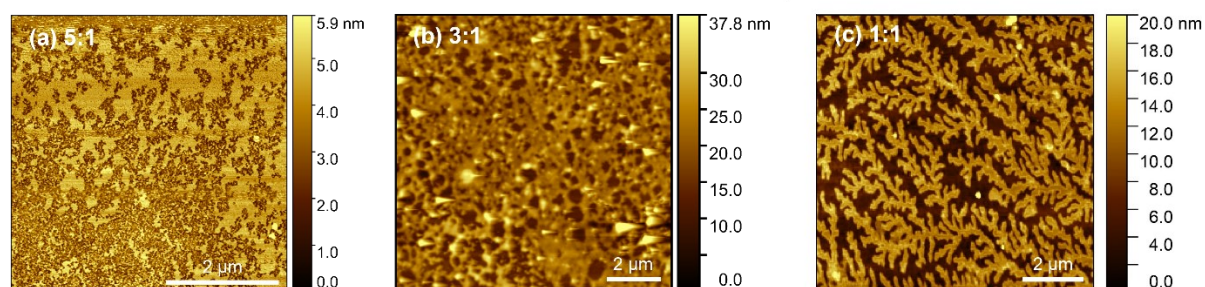


Figure 5-4. Comparison of 5KPF assembled using (a) 5:1; (b) 3:1; (c) 1:1 ratios of THF:H₂O

It is useful at this point to properly define a fractal in order to assess the how appropriate it is to apply this term to the observed morphologies. Fractal dimensions can be ascribed to any truly rough shape such as the coastline of a landmass or the surface of an ocean. The repeating patterns popularly thought of as fractals can be defined as ‘complex patterns that are self-similar across different length scales’.²⁷⁰ To qualify these systems as fractal and bolster the hypothesis of their formation in solution, in particular ruling out drying effects, a bulk analysis technique was required.

5.3.3 - Bulk analysis – Small angle neutron scattering (SANS)

To ascertain to what extent these features might be forming in solution, small angle neutron scattering (SANS) was employed. For SANS measurements were submitted three replicates of the 1:1 samples, containing what should be fractals, one replicate of the 5KPF polymer just in THF and one replicate of a 3:1 sample (where no fractals had been observed by AFM). It should be noted at this point that SANS analysis relies upon contrast in scattering between the material being analysed and the background solvent. A particular source of scattering are the protons of the system and as such use of a deuterated solvent or deuteration of the material itself can greatly increase the quality of data.²⁸⁴ The assembly

and subsequent measurements were therefore conducted using deuterium oxide with hydrogenated THF since the latter was expected to have evaporated by the time of measurement.

When examining the 1:1 data, all 3 replicates can be clearly seen to adopt an ordered, apparently linear on logarithmic axis, pattern (**Figure 5-5**). We therefore found that a basic power law fit the data well. In SANS theory it is known that surface fractals, i.e. the neutrons detect self-similar fractal behaviour on the surface of objects, can be described the following equation known as Porod's law.

$$I(Q) = \frac{A}{Q^D} + B \quad (\text{Eq. 5-1})$$

Where $I(Q)$ is the scattering intensity as a function of Q , a reciprocal space variable, A and B are constants and D is the fractal dimension.²⁸⁴ Rearranging and taking the logarithm of both sides yields:

$$\log(I(q) - B) = \log(A) - D \cdot \log(Q) \quad (\text{Eq. 5-2})$$

Clearly then, a sample exhibiting surface fractal behaviour would expect to yield a straight line given the logarithmic axis. Furthermore, taking the gradient of the line will yield an estimate of the fractal dimension. This gave a mean fractal dimension of 4.033 with a standard deviation of 0.0715 for 5KPF when assembled in the 1:1 condition. In order to be termed fractal behaviour, the linearity must persist for at least an order of magnitude, a property that is also evident in the data shown.²⁸⁴

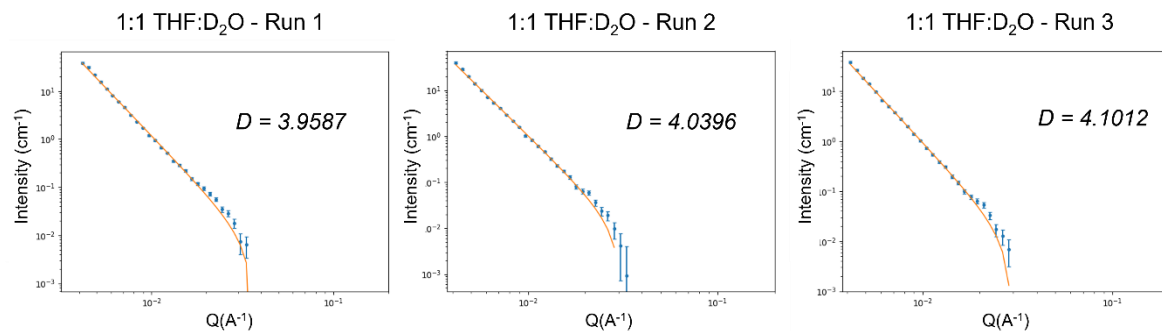


Figure 5-5. Small angle neutron scattering (SANS) data of 5KPF stirred for 3 days in 1:1 THF-d8:H₂O. Using (Eq. 5-2), the fractal dimensions can be estimated from the slopes of the linear fits and are displayed on the figures.

When comparing this data to the 3:1 case a quite different dataset was obtained (**Figure 5-6a**). Rather than being linear the data shows a distinct curvature from 0.5 to $0.01 \text{ \AA}^{-1}$. Possible features that could cause such a shape include flat, 2-dimensional structures particularly ellipsoids.²⁸⁴ The AFM data at this point certainly seemed to suggest smoother, less well-defined morphologies dominate when these conditions are employed. Certainly, to see such a distinct difference between the two samples in solution along with the consistent linearity in 1:1 conditions greatly strengthened our hypothesis of condition-dictated fractal formation in solution. The polymer dissolved in just deuterated THF displayed noisy and disorganised data points that could not be fitted to any model for a particular organised nanostructure (**Figure 5-6b**). This implies the conformation of the polymers in solution is random with no self-assembled and ordered structures present to give a defined scattering profile.²⁸⁴

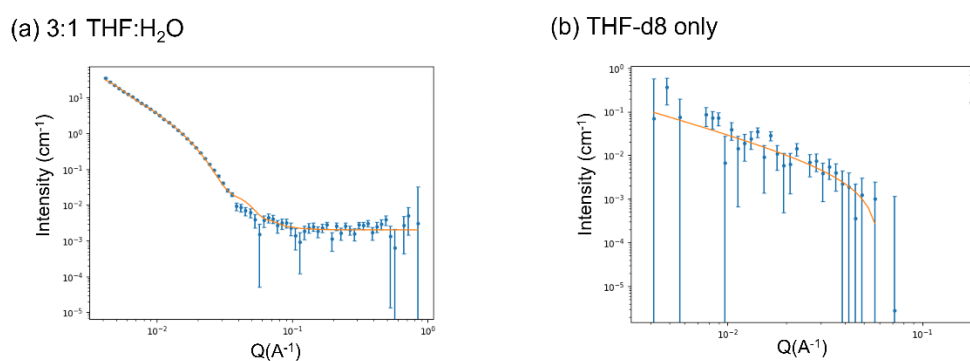


Figure 5-6. Small angle neutron scattering data from 5KPF (a) stirred for 3 days in 3:1 THF:H₂O and (b) just THF-d₈. It is assumed here that the polymer dispersed in THF-d₈ is representative of the case in hydrogenated THF.

5.3.4 - Scanning electron microscopy

To allow for higher throughput sample analysis, scanning electron microscopy (SEM) was employed to image a more comprehensive variable space including volume fraction (i.e. the relative volumes of THF and H₂O used), final concentration and PEG length. Samples were all imaged without prior staining as the semiconducting systems were found to be suitably conductive or thin to avoid charging in an electron beam. Further, to properly explore the variable space, F8BT grafted with 10 kDa PEG chains (10KPF) was now included into the polymer set. This data will ultimately be presented as a phase diagram later but a few comments on the SEM findings will be made first.

Firstly, whilst the AFM data had so far suggested fractals were only present when using 1:1 THF:H₂O conditions, with SEM it was noticed that the volume fractions (i.e. THF:H₂O ratios) and final concentration variables did not actually entirely preclude fractal formation. This initially seemed contradictory to the SANS data that implied non-fractal morphologies in solution (**Figure 5-6a**). However, close inspection of the SEM data revealed the fractal phase appeared to coexist with another globular and less well-defined phase. This disordered phase is highlighted both on its own in **Figure 5-7a** and coexisting with the fractal phase in **Figure 5-7b**. It is unclear at present if this phase precedes or proceeds fractal formation if either. The greater level of insight that could be gained from SEM was due to the ability to rapidly profile much larger segments of a substrate surface. AFM, whilst a method of choice for high resolution images of exceptional quality, can easily give biased impressions of sample morphology through its relatively slow analysis of small substrate cross sections.

SEM also allowed for a broader view of the fractal phenomena. As can be seen from the **Figure 5-7b**, fractals appeared as if they grew outward from denser, nucleating regions and spanned tens of microns with a single uninterrupted network that, for instance, a charge carrier might percolate through.

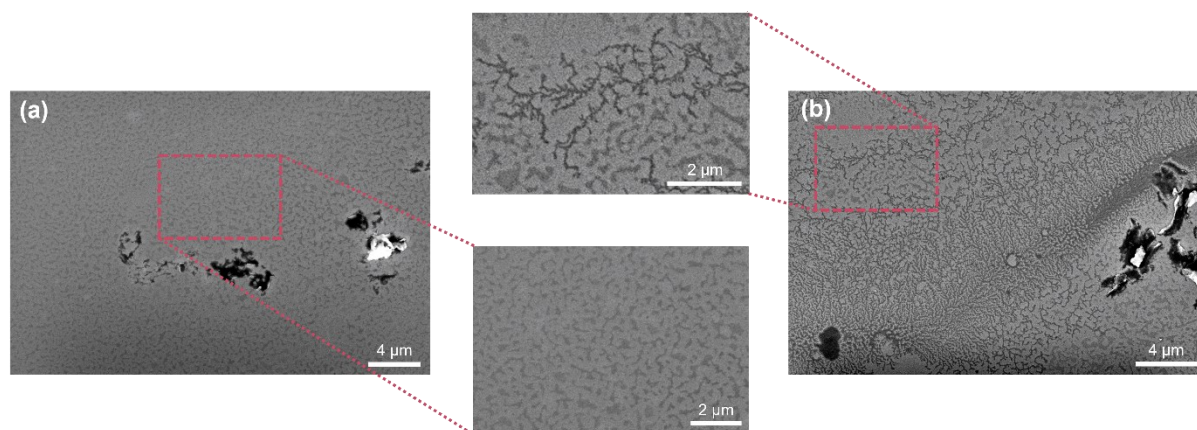


Figure 5-7. Example images from 3:1 THF:H₂O assembly conditions. (a) an instance of the disordered, globular phase and; (b) an illustration of how this coexists with the fractal phase.

As with 5KPF, 10KPF samples again all showed fractal formation regardless of the assembly conditions. Quantitatively, however, the fractals became denser with higher concentration to the extent that the intricacy of their structure began to be compromised by lack of space, a factor that has been shown to limit fractal formation capability.^{167,285}

Whilst 2KPF was unable to produce the intricate fractals seen in 5KPF and 10KPF, all samples did exhibit some 'pseudo'-fractal features. These are structures that have a resemblance to their fractal counterparts but lack the finer morphology and further appear to fragment somewhat. Indeed, as shown in **Figure 5-8**, what might initially appear to be similar phenomenon look quite different when viewed at the same magnification. At present it is speculated that 2KPF might undergo a similar assembly mechanism to 5KPF but, lacking the stability from shorter PEG chains, agglomerates somewhat into less defined, lower surface area mimics of the fractal phase.

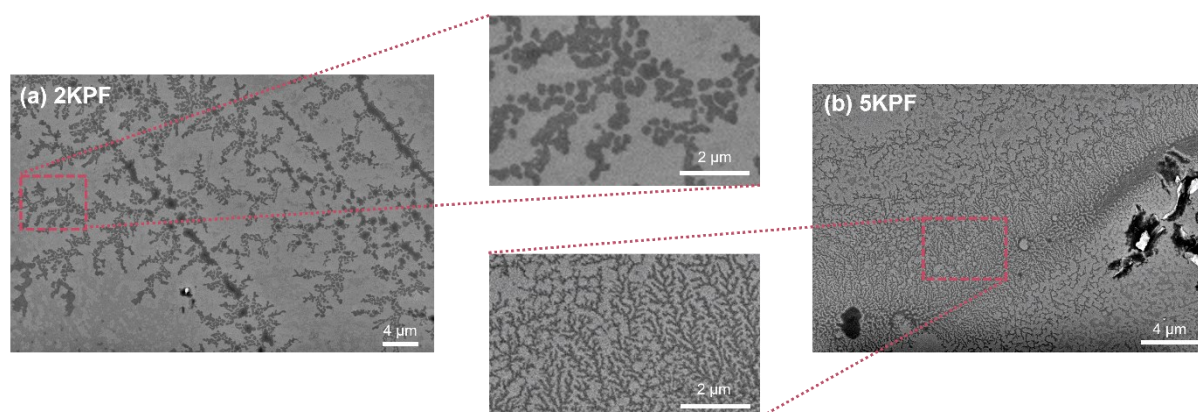


Figure 5-8. SEM images illustrating the difference in apparently similar fractal like morphologies between (a) 2KPF and (b) 5KPF. Taking the images at the same magnification (central images) it can be seen the 5KPF morphology is far more intricately defined.

As shown in **Figure 5-9**, 10KPF formed fractals similar in appearance to those of 5KPF. Use of a steeper solvation gradient (5:1 - THF:water) again showed competition between a globular, less defined phase and an intricate fractal phase (**Figure 5-9a**). Moving toward 1:1 allowed formation of an even mat of F8BT-based fractals (**Figure 5-9b**). That 10KPF behaves in the same way as 5KPF indicates the design space for this phenomena is relatively large and at present seems to show a threshold value of PEG length/hydrophilicity beyond which fractal behaviour becomes energetically favourable.

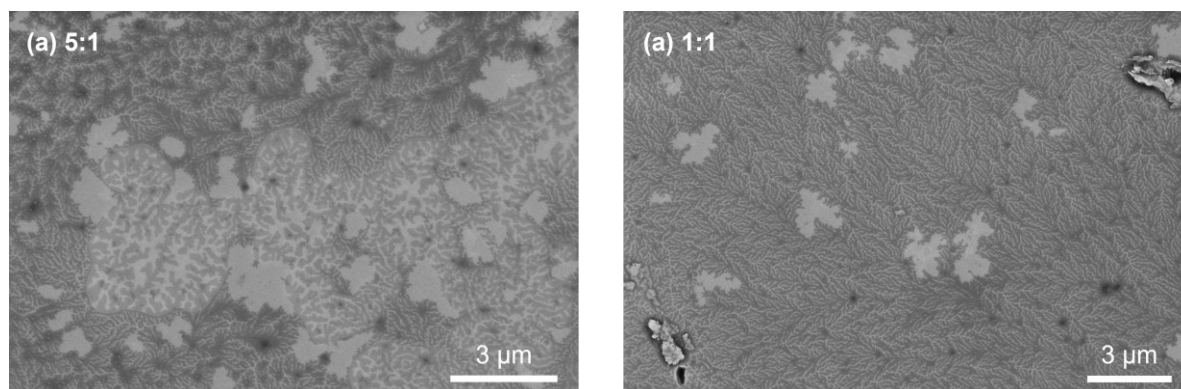


Figure 5-9. SEM images of 10KPF fractals assembled through: (a) 5:1 – THF:water, where 2 phases can be seen, and; (b) 1:1 – THF:water

It is worth noting the globular phase seen with steeper solvation gradients in 5KPF and 10KPF bears resemblance to the fractal-like phase of 2KPF. It seems this competing phase dominates in systems of greater hydrophobicity or assembled through steeper solvation gradients. Further data is required to substantiate such a claim however.

Since fractal morphologies had been seen in all samples of 5KPF and 10KPF regardless of the conditions used, a control was required to test if fractals might form whilst on the substrate and without such a protracted assembly process. To probe this, nanoparticles of 5KPF were prepared via the nanoprecipitation method. This involved quick precipitation of a small volume of concentrated polymer solution (0.1 mL of 5 mg/mL 5KPF) in water (1 mL) followed by nitrogen bubbling to rapidly remove the THF then immediate dilution to image concentration for sample preparation. Such a procedure removes any effects from slow evaporation and would imply the rapid formation of whatever morphologies are observed. Interestingly, SEM revealed NPs nested in an interconnected, fractal-like network (**Figure 5-10**). The origin of fractal formation is still unclear however as the shape of the fractals implies they nucleated from the nanoparticles themselves. This could speed up the fractal formation making it difficult to compare the nano-precipitated system to the slow evaporation.

The main finding of this control is to show how fractal-like morphologies can form rapidly without a slow evaporation method. This could either be occurring immediately after nanoprecipitation or as the sample dries. Certainly though, the slow evaporation protocol is required to create a homogeneous fractal system without the presence of particulates. Further SANS and SEM data is required to properly elucidate the true mechanism.

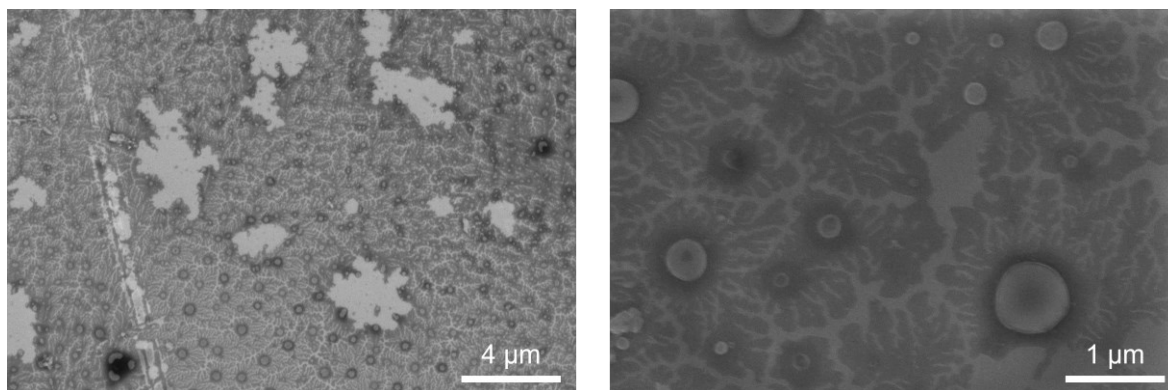


Figure 5-10. SEM images of 5KPEG F8BT prepared through nanoprecipitation.

5.3.5 - Constructing a phase diagram of the fractal assembly

As mentioned, the SEM data was collected systematically to explore a variable space over several axis. The decision as to what variables would be most appropriate came from the following analysis. In diffusion-limited aggregation (DLA) theory it has been shown both theoretically and experimentally that concentration plays an important role in fractal formation. Multiple experimental publications have demonstrated how above a certain concentration the system becomes too crowded precluding fractal-like morphologies.^{167,285} Hence to help elucidate the mechanism, the final concentration in water was included in the parameter space.

In considering how best to represent the meaning of solvent ratio it was decided that an axis describing the initial volume fraction, V_{THF} , of THF was required.

$$V_{THF} = \frac{Vol. \% THF}{Vol. \% Water}$$

This should allow for some quantification as to the extent and gradient of the solvent change i.e. a change from 80% THF ($V_{THF} = 5$) to 100% water is a much more dramatic shift in solvation than 25% THF ($V_{THF} = 0.5$) to 100% water and could have implications as to driving aggregation and assembly. The third axis, and indeed most important, was the length of the grafted PEG chains.

Finally, all particle concentrations would be normalised by F8BT content through UV-visible measurements (see **Figure A 4**) to attempt to match the number of single polymers in solution since

normalising by weight will change particle concentration as a result of the range of PEG chain lengths employed. Therefore, polymer concentration will be presented as a normalised value relative to 5KPF where, for instance, '0.5' corresponds to a concentration that has the same F8BT content by absorption as a 0.5 mg/mL solution of 5KPF in THF.

Following this methodology, the phase diagram shown in **Figure 5-11** was constructed. This figure clearly highlights the main finding of the investigation so far: that the prevailing factor for determining whether fractal-like aggregates are observed is the chain length of the PEG attached. Clearly, between 2 and 5 kDa the energetics of the system shift such that the higher surface area morphologies of fractal-like aggregates can be supported. Despite extensive imaging of each sample, it was not possible to accurately discern a difference between the same polymer with different assembly conditions. Considering the SANS data did exhibit notable differences between $V_{THF} = 3$ and 1 for 5KPF (**Figure 5-5b** vs **c**) it is likely that more subtle changes occur that could not be detected through microscopy analysis. Further SANS experiments are required to confirm this hypothesis.

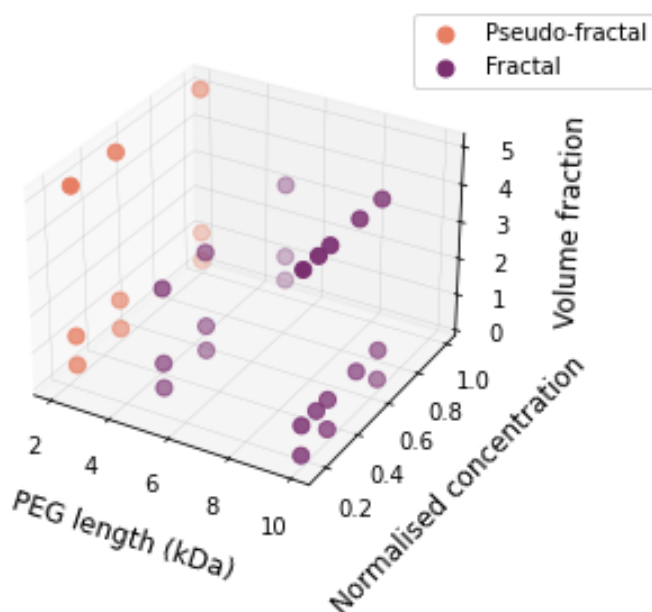


Figure 5-11. Phase diagram evaluating the fractal-like aggregates observed across the variable space of PEG length, normalised concentration and volume fraction. Observations were divided into pseudo-fractals, that mimic fractals but with substantially lower surface intricacy, and fractals.

5.3.6 - Hydrophilicity quantification

To move this work from qualitative observations to the domain of fractal engineering, some general physical properties of the system need to be extracted. With these in hand analogous semiconducting/conducting systems could be tuned according to these properties, hopefully allowing a replication of the fractal phenomenon. Accordingly, experiments are underway to quantify the change in hydrophilicity of the systems with PEG length. Shown below in **Figure 5-12** is a plot of the contact angle measurements observed from MQ water on drop cast films of the respective F8BT derivatives. As expected, the contact angle decreases as the PEG chain length is increased indicating increasing hydrophilicity. Unfortunately, the high PEG content of the polymers made homogeneous film formation challenging, regardless of spin-coating conditions, and it was found drop-casting provided the best coverage. Even then however significant inhomogeneities persisted leading to likely erroneous results, such as that seen for 2 kDa where the water likely contacted mainly with the glass substrate. The experiments are ongoing to increase confidence in the values but an initial outline of the energetic landscape has been drawn.

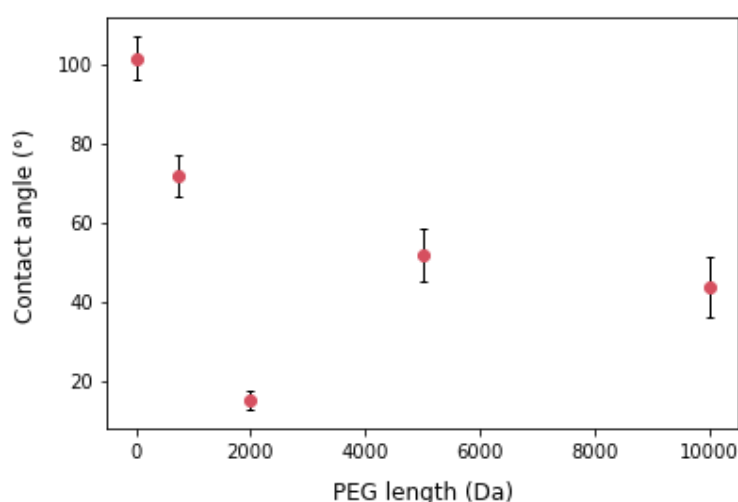


Figure 5-12. Plot of contact angle with PEG chain length. Error bars show the standard deviation of the data. The values recorded for 2000 Da are thought to be incorrect and result from the poor homogeneity of the film, despite multiple attempts.

From here the focus will be to explore hydrophilicities in the gap between 2 and 5 kDa PEG chains, the region in which a transition to well defined fractals can be seen as discussed previously. To complement this, experiments are planned to measure the octanol partition coefficients of the polymers, another commonly used method to quantify hydrophilicity.²⁸⁶ Hereafter, the general relevance of the quantities extracted will be tested through attaching PEG to other semiconducting polymer backbones, tuning their hydrophilicity to these parameters and ascertaining if fractal formation is generalisable.

5.3.7 - Upcoming analysis

To further our understanding of the system, cryo-TEM measurements are to be performed. It is anticipated that these will elucidate the extent to which the fractal aggregates exist in solution. Regrettably, repeated delays from equipment/facility issues will mean the data will be collected after thesis submission. Further SANS analysis will also be performed in the upcoming planned beamtime. Measurements on systems of different PEG lengths, nano-precipitated procedures and stability to temperature changes should greatly aid our comprehension of the phenomenon.

5.3.8 - Simulation and possible mechanisms

As the fractal assembly phenomenon is explored it was thought prudent to consider possible simulations that might be run in tandem to support any hypotheses that emerged as to the mechanism and dominating variable in the system. It was further postulated that if transition to a fractal regime were found to be abrupt with respect to increasing PEG chain length, such a threshold point might allow the extraction of physics that could be of use to fields concerned with nonlinear dynamics and theories modelling apparent ordering from chaos.

Diffusion-limited aggregation (DLA) theory is a modelling approach used to simulate the formation of fractals from spherical units. The basic theory describes a collection of spheres that each will migrate through Brownian motion. As illustrated in **Figure 5-13**, when one particle comes within a predefined range of another, the two will be joined by the surface closest to one another. The sequential addition of particles to each other in a diffusion limited regime yields the formation of continuously branched structures with subsequent particles far more likely to add to the branches than penetrate deep into the structure. These architectures quickly take on a fractal geometry and indeed are confirmed mathematically as such.^{278, 279}

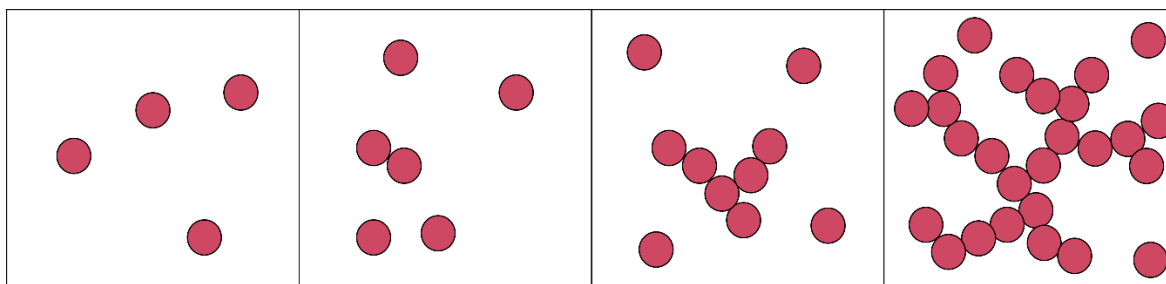


Figure 5-13. Schematic representation of the diffusion-limited aggregation assembly mechanism

Given the extensive modelling precedent in the literature, efforts were made to develop a basic simulation of the F8BT-PEG system in an attempt to better understand this phenomenon. Early approaches to this end have shown some promise.

The first main challenge in modelling such a system is in deciding what an appropriate approximation of a single graft copolymer would be. An option that would simplify the problem would be to model them as spheres thereby allowing for a traditional DLA approach to be pursued. This initially did not seem unreasonable since the polymers can be readily shown to collapse into spherical aggregates when exposed to water in the nano-precipitation methodology. Given the estimated Mw of close to 200 kDa, a rough, back of the envelope calculation puts the extended polymer length at around 4-500 nm for just the backbone. The intricacy of fractal structures observed so far would require spheres on the 50 nm length scale (**Figure 5-14**). Whilst this is feasible it was decided a better starting point would be a model that tried to incorporate the hydrophobic/hydrophilic and graft copolymer nature of PEG-F8BT to explore how the changing ratio of the former might increase surface area and tend the system toward fractal-like morphologies. A model based on spherical building blocks may be revisited in the near future however.

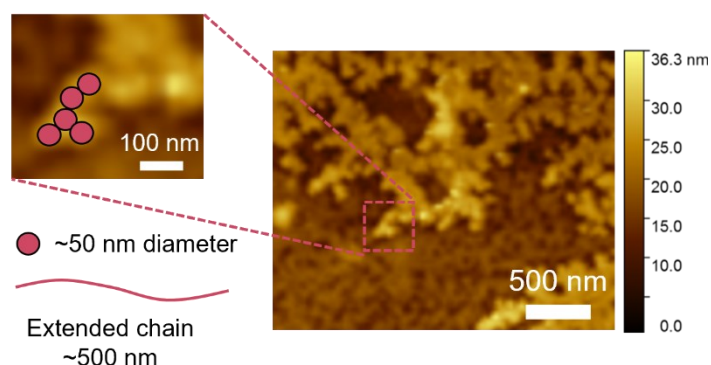


Figure 5-14. Superimposition of spheres on AFM data to assess applicability of this approximation. It can be seen spheres of around 50 nm diameter would be required to build the morphologies observed here. For reference an estimate of the extended chain length is also presented.

Therefore, taking a ‘bead necklace’ approach, a system was created where each polymer was represented as a series of beads with a solvo-phobic bead situated between chains of solvo-philic beads (**Figure 5-15a**). The simulation was run as a hybrid incorporating standard DLA rules along with the inclusion of a solvent molecule that is -phobic or -philic to the beads in the chain. Pleasingly, as the chain length of the solvo-philic segment was extended, the system evolved from resembling a tightly bound aggregate to a branched chain structure reminiscent of fractals (**Figure 5-15b**). This was encouraging since the solvent molecule being an analogue for water demonstrated a transition toward higher surface area, fractal-like morphologies as the proportion of solvo/hydrophilicity was increased.

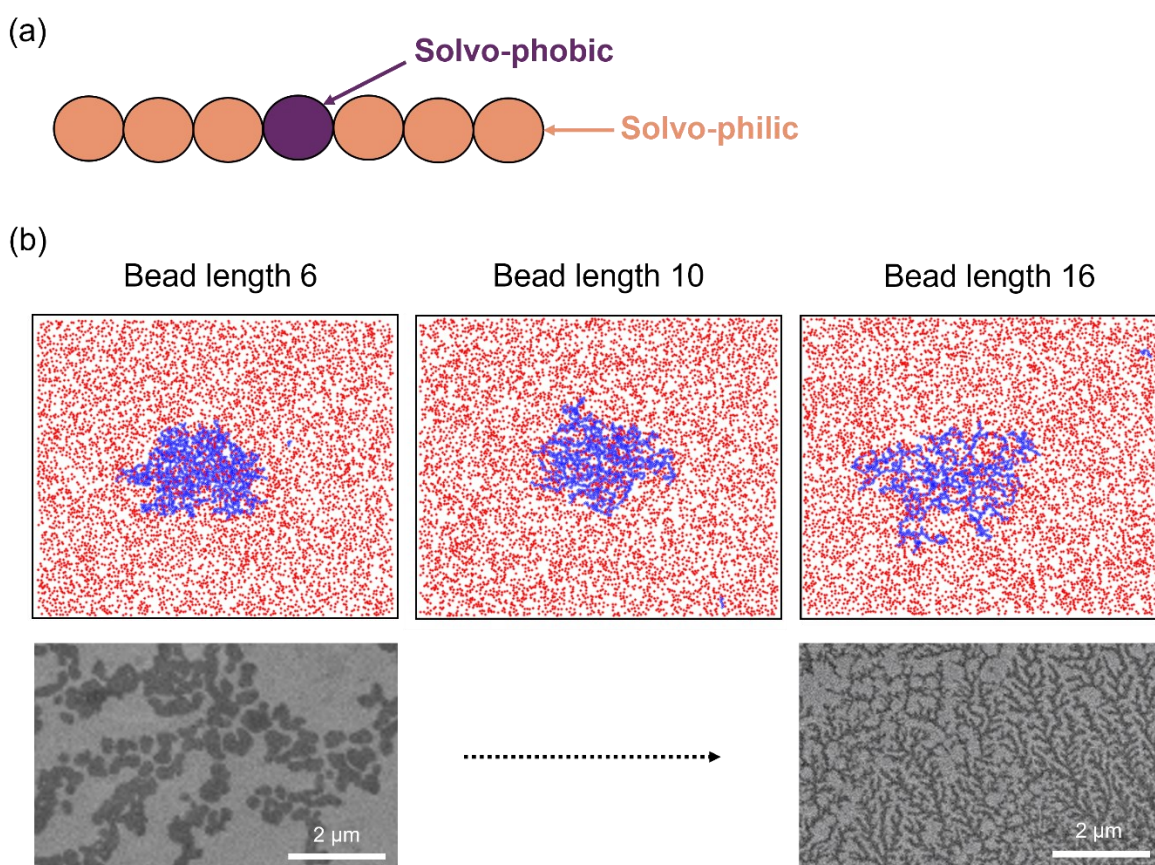


Figure 5-15. (a) Schematic of the bead necklace model used to approximate the graft polymer system (b) DLA-based simulations show a movement towards fractal-like aggregates with increasing solvo/hydrophilic chain length. The SEM images shown below the simulations highlight possible similarities as the move from 2KPF to 5KPF shifts from globular to fractal-like aggregates.

Though this model is highly simplistic it includes, to the best of our knowledge, the first hybridisation between DLA and solvophobic/philic models. It also helps suggest that fractal geometry can be engineered through tuning of the hydrophobic and hydrophilic domain ratios in a single graft polymer. If such a general design rule can be transplanted to an analogous system this would provide access to a form of 'fractal engineering' that, whether occurring on the substrate or in solution, could be of great interest to a range of device or biological applications where intricate, high surface area morphologies with percolation pathways beyond 10s of μm are desired.

It is worth mentioning, given the, albeit gentle, stirring employed so far, if fractals form during the slow evaporation it is difficult to argue our system exists purely in the diffusive regime and likely includes some additional kinetic component to the particle motion. When the aggregation of particles is modelled with linear trajectories instead of random walks it is known as *ballistic aggregation* (BA). Like DLA, ballistic aggregation gives rise to fractals though with a denser branching structure.²⁸⁰ As further SANS and microscopy data is gathered it is hoped to elucidate where the assembly is occurring (in solution vs on the substrate). If it appears to happen during stirring, then incorporation of an extra kinetic component for a BA-derived model will be considered.

5.4 - Conclusions and future work

Fractal formation from F8BT-based semiconducting polymers has been reproducibly demonstrated. Small angle neutron scattering (SANS) bulk analysis has indicated these structures form in solution and suggested a dependence to amplify or suppress a secondary, less intricate phase on the assembly conditions. Extensive batch analysis exploring a substantial volume of the assembly variable space has been undertaken revealing, at least through microscopy, less reliance on the specifics of assembly but substantial dependence on the PEG length. Moving from a graft PEG length of 2 kDa to 5 kDa yields a transition from a globular, vaguely fractal-like system to an intricate, high surface area fractal-like system. Increasing the PEG length still further preserves the phenomenon implying a large design space beyond a threshold value for fractal assembly. The phenomenon is tentatively explained in terms of the hydrophilic/hydrophobic ratios of the systems through water contact angle and a DLA-based solvophilic/phobic hybrid model.

Moving forward, more PEG lengths may be investigated between 2 kDa and 5kDa to get a more accurate idea of where this transition point occurs. Further characterisation of the hydrophilicity will be undertaken through octanol partition coefficients estimations and further contact angle experiments. General design rules will look to be extracted from this system through implementation

of the same chemistry on similarly hydrophobic yet optoelectronically contrasting semiconductors such as other F8BT derivatives, polythiophene (PT), benzodithiophenedione (BDD) and indacenedithiophene (IDT)-based polymers.

At the same time, ways to encapsulate these observations into a more sophisticated simulation to better interpret the phenomena will be pursued. It is hoped the model might allow at least estimation of some physical values pertaining to the thermodynamics of the system. Outlining of the thermodynamic landscape that favours fractal formation could prove to be a useful toolbox for future attempts at fractal engineering whether in the realm of semiconducting polymers or beyond. Indeed, the dendritic nature of charge transporting tissue such as neural networks may form more complex interfaces with such materials allowing for a greater intricacy in neuro-polymer contact. It is further hoped such morphologies will have applications in bulk heterojunctions where a high surface area interface between donor and acceptor yet long percolation pathways for electrons and holes is desired.

5.5 - Experimental section

5.5.1 - General comments

All details not included here regarding material and characterisation can be found in the general experimental section of Appendix I.

5.5.2 - Simulations

The following description was provided and undertaken by Dr. Srikanth Ravipati. Simulations were performed using conventional diffusion limited aggregation theory. A number of spheres were defined as a 'bead necklace' and given flexibility between each constituent. A solvent molecule is defined at an appropriate density to simulate water, the beads of the necklace are defined as either being loving (solvophilic) or hating (solvophobic) of this explicit solvent. A seed molecule is placed at the centre of the simulation to act as a point of growth for the simulation. Monte-Carlo loop is invoked. In every iteration of the loop:

1. Solvent or solute type is chosen randomly.
2. If solvent is the chosen type, a random solvent molecule is selected and randomly displaced from its current position.
3. If solute is the chosen type, a move is randomly chosen from the possible moves: displacement, reposition, and regrowth
4. The attempted move is rejected if there is an overlap in the new configuration. If the new configuration is overlap free, the attempted move is accepted with the criteria where $\Delta u = u_{new} - u_{old}$ is the energy change between the new and the old configuration. As in the primitive model, if the solute diffuses out of radius-of-injection, the solute molecule is deleted. If the solute approaches the seed at the centre, it becomes part of the seed and contributes to the seed growth. In both cases, a new solute molecule is introduced at the radius-of-injection.
5. The Monte-Carlo loop is terminated upon reaching a pre-set number of iterations or upon the growth of the seed cluster to a pre-set radius

In our model, following the explicit consideration of the solvent, pair potential is defined between beads of the solute and solvent, as well as between solvent and solvent. For the sake of simplicity, intramolecular and intermolecular interactions among the solute beads are modelled via simple hard-core interactions. Hard-core potential is characterised by only one parameter σ (hard-core diameter) and is given by:

$$u(r) = 0 \text{ if } r > \sigma, \text{ else } \infty$$

Where u is the pair potential and r is the pairwise distance between two entities. In addition, the interaction between beads represented by colour filled circles and the solvent is also characterised by hard-core potential.

Solvent-solvent interactions and the interactions between beads are represented by open circles and solvents are characterised by Lennard-Jones potential that is given by

$$u(r) = 4\varepsilon \left[\left(\frac{\sigma}{r} \right)^{12} - \left(\frac{\sigma}{r} \right)^6 \right]$$

where, ε is the potential depth and σ is the distance at which the potential is zero. Simulations are performed in reduced units for the sake of convenience. In case of reduced units scaling is done as

$$u^* = \frac{u}{\varepsilon} \text{ and } r^* = \frac{r}{\sigma}$$

With this scaling the hard-core potential in reduced units is

$$u^*(r^*) = 0 \text{ if } r^* > 1.0, \text{ else } \infty$$

and the Lennard-Jones potential in reduced units is

$$u^* = 4 \left[\left(\frac{1}{r^*} \right)^{12} - \left(\frac{1}{r^*} \right)^6 \right]$$

Relatively speaking, the beads that interact with the solvent via Lennard-Jones (LJ) potential are hydrophilic compared to the beads that interact with the solvent via the hard-core potential. Solvent is modelled as a monomer and solvent-solvent molecules interact via the Lennard-Jones potential. A simulation cell of 600x600 is considered with 6000 solvent molecules to run our model with explicit solvent and fully flexible poly-bead solute. Hard-core interactions between solute beads are characterised by $\sigma^* = 1.0$. Solvent-solvent LJ potential is characterised by $\sigma^* = 2.0$ and $\epsilon^* = 1.0$. Solvent and hydrophilic bead LJ potential is characterised by $\sigma^* = 1.0$ and $\epsilon^* = 1.0$. Solvent and hydrophobic bead hard-core potential is characterised by $\sigma^* = 1.0$, and the reduced temperature is $T^* = k_B T / \epsilon$. A prototype simulation of our model with these settings was used with 5×10^6 Monte-Carlo steps.

5.5.3 - Assembly Protocol

To establish concentrations, all samples were normalised to the 5 kDa PEG F8BT sample. It was assumed the amount of PEG present would not change in the absorbance of the F8BT backbone and as such a normalised absorption of '0.5' would correspond to a polymer having the same F8BT content by absorption as the 5 kDa PEG F8BT at a concentration of 0.5 mg/ml. This was ascertained using the peak at 446 nm (see **Figure A 4**).

For assembly, in a typical experiment a THF polymer solution of concentration as specified above was prepared and sonicated for 10 minutes. The concentrations were calculated such that the concentration after the experiments were 1, 0.5 or 0.25 (no units since normalised – see above). To separate 2 mL vials was added 0.3 mL of MQ water, a clean stirring bar and the THF polymer solution (0.06 mL for 1:5; 0.3 mL for 1:1; 1.5 mL for 5:1 of THF:Water). The vials were covered with punctured parafilm and stirred at the lowest setting for 3 days to allow all THF to evaporate. Following this stirring was stopped and the sample diluted to 1/5th of the 0.5 normalised concentration i.e. 0.1 mg/mL in the case of 5 kDa PEG F8BT and all other polymers normalised by absorption to this F8BT content.

5.5.4 - Microscopy

5.5.4.1 - Atomic force microscopy (AFM)

Measurements were performed on a 5500 Agilent AFM using an AC240TS-R3 cantilever from Oxford Instruments ($f = 70$ kHz, $k = 2$ N/m, no tip coating) with AC tapping mode in air. Typically, substrates were prepared on Si by diluting down to $1/5^{\text{th}}$ of the 1:1 concentration (after THF evaporation) then applying 5-10 μl to the surface for 10-20 minutes following which a Kimwipe was used to wick off remaining liquid. Samples were imaged within 48 hours of preparation.

5.5.4.2 - Scanning electron microscopy (SEM)

Measurements were taken on a Zeiss Leo 1525. Silicon substrates were prepared by sonication in acetone for 15 minutes followed by nitrogen drying. Typically, substrates were prepared on Si by diluting down to 0.1 (normalised concentration – see above) then applying 5-10 μl to the surface for 10-20 minutes following which a Kimwipe was used to wick off remaining liquid. Samples were imaged within 48 hours of preparation. Owing to the poor visibility of such small features, images were often enhanced using a high pass filter to increase the contrast on the software GIMP.

5.5.5 - Additional characterisation

5.5.5.1 - Small angle neutron scattering (SANS)

Measurements were performed in 0.1-0.2 mm pathlength quartz cuvettes by James Douth at the ISIS neutron and muon source. Just before measurement, samples were diluted to $1/5^{\text{th}}$ of the 1:1 concentration (as was carried out for AFM).

5.5.5.2 - Contact angle measurements

Measurements were made on an Ossila contact angle set up. Glass substrates were used after cutting into squares (10x10 mm), sonicating with detergent, deionised water, acetone and isopropyl alcohol then drying under nitrogen flow. To these were applied the polymers in THF at concentrations

between 0.5-3 mg/mL by drop casting. The solutions were reapplied until an even covering was observed. A pipette was clamped ~2 cm from the surface of the substrate from which 12 μ L of MQ water was dropped. Images were then taken 30 seconds after impact with surface and analysed with the Ossila contact angle software. For each sample 2-4 measurements were taken, the mean and standard deviation of these is plotted in the main text.

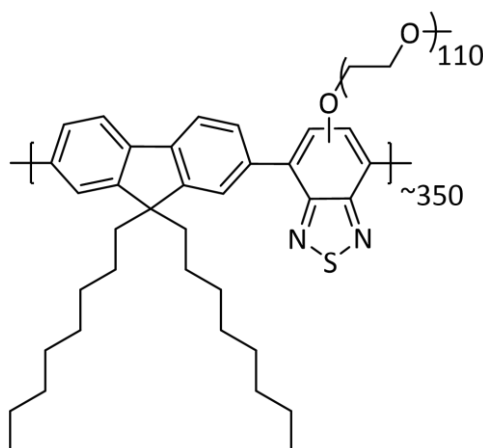
5.5.6 - Synthesis

5.5.6.1 - F8BT-PEG general protocol

To a microwave vial was added the fluorinated F8BT (2.8 mg, 1 eq.), freshly ground NaOH (11.6 mg, 40 eq.), a stirring bar and the vial sealed under argon. In a separate microwave vial was added the PEG (258.3 mg for 10 kDa, 5 eq.), a stirring bar and vial sealed under argon. A stock of 0.75 mL CB and 0.25 mL DMF was made up which was split between the two vials. The F8BT solution was heated to 120 °C and stirred for 10 minutes. At this point PEG was added and solution stirred, again at 120 °C, overnight. Depending on the length of the PEG chain, the crude was then either precipitated and washed in water or dialysed (15 kDa cutoff) for 3-4 days. NMR analysis then confirmed the correct ratio of PEG to F8BT protons and absence of fluorine. Most polymers were supplied by Dr Adam Creamer already characterised however 10KPEG-F8BT was made by the author for this project and as such the NMR data is given below.

All other polymers used in this chapter were synthesised by Dr. Adam Creamer in accordance with his paper on the subject.²⁸²

10KPEG-F8BT: 10 000 Poly(ethylene glycol) – Poly(9,9-dioctylfluorene-*alt*-benzothiadiazole)



^1H NMR spectral data was consistent with those reported previously.²⁸² ^1H NMR (400 MHz, CDCl_3): δ = 7.94 (7H, m, aromatic protons), 3.63 (888H, br, PEG chain), 1.25 (34H, br, alkyl chains)

Chapter 6 - Conclusions and future work

In this work the aim was to produce new, innovative forms of semi/conducting polymers, primarily poly(3,4-ethylenedioxythiophene) (PEDOT) for use in biomedical applications. This has been achieved via a number of avenues. In the first half of the thesis, Chapters 2-3 have focused on adding complexity to covalent polymeric PEDOT derivatives. This has involved the exploration of degradable PEDOT derivative designs in Chapter 2 as well as fabrication of functional variations for use in biomedical applications such as organic electrochemical transistors (OECTs) or printable bioelectronics. In the latter half of the thesis, supramolecular systems have been explored both with 3,4-ethylenedioxythiophene (EDOT) and poly(9,9-dioctylfluorene-*alt*-benzothiadiazole) (F8BT) derivatives. The self-assembly of EDOT-peptides into nanofiber-based hydrogels is explored in Chapter 4 and then assembly of F8BT into fractals with the possibility to generalise to other polymeric systems (including PEDOT) is discussed in Chapter 5.

Chapter 2 addresses the problem of the lack of biodegradation of PEDOT. Here, several designs that install degradable linking moieties into a PEDOT backbone were presented. The initial design was successfully fabricated via a catalyst free reaction yielding oligo-EDOT-based polyesters with molecular weights over 200 kDa. These polymers were fully characterised with 4-point probe measurements suggesting conductivities in the range of 10^{-2} - 10^{-4} S/cm, though inhomogeneities in film formation limited the accuracy of such measurements. In the context of the literature, this gives the materials some of the highest conductivity values for both 'type I' and 'type II' degradable conductive polymers.¹⁴¹ It should further be noted that consideration was placed in the design of the degradation products. An issue rarely given due attention is how soluble and therefore how easily excretable these materials might be after degradation. In the case of EPE(HD)-*co*-TG the degradation products after a hydrolysis mechanism would consist of a partially water soluble di-acid and triethylene glycol.

A limitation met by this early design was the hydrophobicity that appeared to greatly limit the rate of any degradation. Indeed, in the research undertaken so far, only hydrogen peroxide showed evidence of producing degradation. To both combat the hydrophobicity of the system and the lack of self-doping, a new design was presented incorporating a peripheral alkyl sulfonate. Though initial attempts to create these polymers through oxidative polymerisation methods were met with problems in degradable linker insertion from differences in oxidation potential, a subsequent synthetic pathway

was conceived that involved use of direct(hetero) arylation polymerisation (DHAP) chemistry. Use of this route is currently underway.

The future of the research discussed in Chapter 2 will focus on completion of the final design. Given literature precedent and experiments done in the lab with analogous systems, the success of this final DHAP methodology seems likely. At this point, what is expected to be a highly water processable polymeric system will be tested for degradation using the improved methods of analysis detailed in the main text involving dialysis membrane incubation. With a proof of concept in place, further experiments will be planned to assess the rate of degradation, providing meaningful information as to the expected lifetime of structures built from such a material *in vivo*. In parallel the system will be fully optoelectronically characterised and the conductivity ascertained through four-point probe and impedance analysis. To prove this material suitable for *in vivo* applications, the biocompatibility will be assessed through cytotoxicity assays with relevant cell lines such as neural or cardiac cell types. Finally, given the chemical similarity to conventional PEDOT:PSS, the wealth of literature devoted to create intricate morphologies for this gold standard will be applied to our system. This could include hydrogels through de/rehydration cycles¹⁰⁰ or porous scaffolds through slow, controlled freezing and lyophilisation.⁹²

In Chapter 3 efforts towards developing novel EDOT/3,4-propylenedioxythiophene (ProDOT) monomer are detailed and the challenges outlined. From here the efforts undertaken so far to create new functional derivatives of PEDOT are explained, the progress critically analysed and the required next steps explored. A small library of polymers was created and although some have only reached modest molecular weights, it is anticipated that larger reaction scales and greater care in reagent purity will allow preparation of polymers with sufficient lengths for the desired applications. It is worth considering, however, that beyond a certain length the conjugation will naturally be interrupted by backbone twisting and as such it could be argued polymers of a particularly high molecular weight (> 50 kDa) might not be required.

For polymers designed for printable application, preliminary experiments have been undertaken to polymerise poly(ϵ -caprolactone) (PCL) off-pendant hydroxyl groups from the PEDOT derivative backbone. A current challenge being tackled is proving PCL growth occurs from the polymer itself or whether it is erroneously initiated by residual water in the system, a constant risk with this chemistry.

New approaches to better employ PEDOT and its derivatives for printing applications have begun to emerge in recent years. For instance, the printing of PEDOT:PSS dispersions via ink jet techniques has achieved resolutions down to 30 μm .^{215,216} Additionally, designs are emerging that employ a similar strategy to that presented in the thesis of PEDOT graft copolymer derivatisation. Here the authors

grafted polylactide (PLA) to an EDOT monomer and oxidatively copolymerised with an unfunctionalized EDOT monomer with subsequent printing using direct ink writing. However, a resolution of only 200 μm was reported limiting the intricacy of morphologies that might be prepared for complex cell-based studies. The polymers presented here, coupled with the emerging expertise in the group are hoped to achieve resolutions well below those reported previously to provide conductive, 3D printed systems with controlled nano-topography.

PEDOT doped with a variety of molecules/polymers such as PSS has been commonly employed in OECT applications, but its lack of functionality impedes conjugation of biomolecules to the polymer surface.^{287,288} To improve in this space a structure was derived from recent work in Reynolds' group that demonstrated PEDOT derivatives appended with triethylene glycol monomethyl ether moieties as excellent candidates for OECT materials.⁶⁴ Our system aims to add complexity to this by decorating the backbone with hydroxyl or azide residues for subsequent biomolecule conjugation. Short polymers to this effect are demonstrated using similar steps to the printable polymer work that is planned to increase molecular weight in the near future. It is anticipated these materials will serve as ideal starting points for bioconjugation and subsequent analyte detection through OECT architectures.

In Chapter 4 attention was turned to supramolecular systems of PEDOT/EDOT. The EDOT moiety was shown to be incorporated into a low molecular weight gelator (LMWG) architecture for the first time to the best of our knowledge. Several peptide sequences were studied, three of which showed gelation capacity. A structure-property investigation of these systems was undertaken with elucidation through rheology, atomic force microscopy, pH profiling, UV-vis absorption, extinction coefficient and small angle X-ray scattering (SAXS) analysis. Three examples were seen to assemble into nanofibrous networks in response to the slow pH switch generated by glucono- δ -lactone (GdL). The compounds were observed to assemble differently as a function of the sequence used. The more planar, aromatic triphenylalanine sequence showed earlier signs of fibre assembly, even at basic pH whilst GFF and GFFD transitioned from micelles and formed tightly bundled fibres more slowly. The greatest storage modulus of the final gel was found to come from EDOT-GFF, at around 35 kPa (at 10 mM), a value approaching that of soft tissue.²⁵⁵ The greater flexibility offered by the glycine coupled with hydrophobicity of the following diphenylalanine was thought to be responsible giving a more tightly bundled and stronger fibre network that shows this storage modulus value.¹⁷³ This work sits in line with the large body of literature to date on LMWGs, with assembly mechanisms and details of structure-property relationship being readily rationalised through and consistent with previous work.^{169,173,234,259}

Looking forward, these design rules will look to be utilised in compounds of longer EDOT lengths such as dimer and trimers. Although not reported here, successful synthesis of dimeric and trimeric systems have already been achieved and the assembly of such molecules is under investigation. An area not covered sufficiently at present is the aspect of charge transport. A combination of impedance spectroscopy, wet and dry four-point probe measurements will be undertaken to properly separate electronic and ionic contributions to the conductivity. It is anticipated that the suitable mechanical properties coupled with charge transport will yield a material highly suited for *in vivo* biomedical applications. As such cytotoxicity experiments will also be conducted on the materials to assess their biocompatibility. The novelty of the work so far is the first employment of an EDOT capping group however it is anticipated the longer oligoEDOT-peptides planned will yield materials of even greater interest that will contribute to the conductive soft materials space for biomedical applications.

In the final chapter of this thesis the assembly of a different semiconducting system is explored. It is shown that under certain conditions, substrate-spanning fractal morphologies are observed from a PEG-F8BT brush copolymer. A library of polymers with differing PEG chain lengths are investigated (0.75, 2, 5, 10 kDa). The phenomenon is thoroughly investigated through AFM, scanning electron microscopy (SEM) and small angle neutron scattering (SANS) with the most important factor appearing to be the length of the PEG chain attached to the F8BT periphery. It was seen that between 2 and 5 kDa the system moved from producing pseudo-fractal to intricate fractal features. This transition was hypothesised to occur as a function of the hydrophilicity and therefore surface energy of the systems. It was thought that beyond a threshold hydrophilicity the materials become stable in an intricate fractal state with such a large, exposed surface area. In line with this, preliminary attempts to quantify the hydrophilicity of the polymer series are shown through contact angle measurements. A limitation is the difficulty in forming homogeneous films from the highly PEGylated samples, with the exposure of the substrate biasing the result as was seen in the 2 kDa case. Whether the assembly occurs in solution or during sample preparation on a silicon substrate is still under investigation with SANS data indicating the former but SEM suggesting the latter. Further SANS experiments along with cryogenic transmission electron microscopy (cryo-TEM) measurements will aid in properly answering this in due course.

Finally, simulations of the fractal system were also presented. Although relatively simple these models were able to show a movement from globular to intricate fractal morphologies with increasing amount of solvo-philicity (a replacement for hydrophilicity in the model) and are, to the best of our knowledge, the first hybridisation of diffusion limited aggregation (DLA) theory and an explicit solvent system simulating hydrophobicity/philicity. The literature context for such research is unsurprisingly sparse. Examples of controlled fractal formation can be found in DNA,²⁷⁶ peptides²⁷⁵ and proteins^{274,277}

through careful consideration of structural factors such as host-guest interactions. More specifically however there appears to be only one truly comparable publication that the used an organic semiconducting polymeric system with any degree of control.¹⁶⁷ Here it is control of the polymerisation process through ring opening metathesis polymerisation (ROMP) that brings about fractal formation.¹⁶⁷ However, these features appear to be very small and lack the substrate spanning magnitude of the morphologies observed in this thesis. Further, it was unclear how generalisable such a method might be to other semiconducting polymers.

Moving forward, the space between 2 and 5 kDa will be explored further through synthesis of 3 and 4 kDa PEG F8BT derivatives. More accurate quantification of the hydrophilicity of the polymers will be gained through further contact angle measurements and other methods such as octanol partition coefficient experiments. With this design space mapped somewhat quantitatively, other semiconducting polymer systems will be subjected to the same process of PEG tethering and testing for fractal formation. It is hoped that such analogous systems will demonstrate fractal formation in the same design space, allowing for a statement describing the global energetic requirements for fractal formation and a first step into a form of fractal engineering. Although more abstract than the other research in this work, the fractal geometry of such systems is not dissimilar to that seen in charge transporting tissue such as neural networks. It is therefore possible these materials might prove useful not only in bulk heterojunction applications as donor/acceptors with high percolation pathways but also as complex interface materials with neural tissue environments.

This work set out to explore functional and innovative derivatives of semi/conductive systems, primarily PEDOT, for better integration and utility in biomedical applications. Through a range of avenues, including imbuing degradation, appending functionality, self-assembly into nano-fibre hydrogels and complex fractal patterns, this has indeed been achieved. As mentioned above there is still work to do in order to best present the various contributions to the field of functional biomaterials. However, the groundwork has been thoroughly laid throughout this thesis with project completion anticipated to be, in most cases, a matter of course.

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Chapter 7 - Appendices

7.1 - Appendix I – General experimental details

7.1.1 - Materials

All materials were purchased from Sigma-aldrich, Alfa Aesar, VWR or TCI unless stated otherwise. All reagents were used as received with no further purification unless stated otherwise. Starting materials are detailed below:

Chapter 2: 3,4-ethylenedioxythiophene (EDOT) was purchased from Alfa Aesar. Hydroxymethyl EDOT was purchased from Sigma-Aldrich.

Chapter 3: 3,4-dimethoxythiophene starting material was purchased from Fluorochem. 4-Iodobenzenesulfonyl chloride was purchased from Alfa Aesar.

Chapter 4: 2-Chlorotriyl chloride resin was purchased from Chem-Impex Int'l INC. HATU (O-(7-Aza-1H-benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium) was purchased from Alfa Aesar. All amino acids were purchased from Sigma-Aldrich.

Chapter 5: Fluorinated poly(9,9-dioctylfluorene-*alt*-benzothiadiazole) (F8BT) for polyethylene glycol (PEG) attachment was supplied by another researcher in the lab and prepared using published methods. All water used for assembly experiments was taken from a MQ dispenser. Deuterated THF for small angle neutron scattering (SANS) was purchased from Sigma-Aldrich

7.1.2 - Characterisation and simulations

Nuclear magnetic resonance (NMR) spectra were obtained using either a 400Hz Bruker Autosampler or 400Hz Jeol Autosampler. Unless otherwise stated all measurements were made at room temperature. Mass spectroscopy data was collected using an Agilent **liquid chromatograph mass spectroscopy (LC-MS)** run with Water/MeCN in acidic conditions (0.1 % formic acid). Material was frequently **purified** on a Buchi auto flash column using prepacked Ecoflex silica columns ranging from 12-40 g. **Gel permeation chromatography (GPC)** was generally used to ascertain molecular weight in DMF with 0.05% LiBr by comparison with poly(methyl methacrylate) of a narrow dispersity.

UV-visible spectroscopy (UV-vis) was measured using a Nanodrop 2000c Spectrometer. Samples were measured in quartz and sometimes optical glass cuvettes with pathlengths ranging from 0.1 to 2 mm.

Photoluminescence (PL) was conducted on a using quartz cuvettes with volumes. **Cyclic voltammetry (CV)** data was collected in 0.1 M Tetrabutylammonium perchlorate (TBAP) in acetonitrile. A thin film was deposited using 5 μ l of a $\sim$ 1 mg/mL solution on a glassy carbon electrode with a platinum counter electrode and Ag/Ag⁺ reference. At the conclusion of every experiment, ferrocene was added to the electrolyte and the CV trace of this collected to be subtracted from the working electrode data. To

move from Ag/Ag⁺ to Fe/Fe⁺ the redox potential of ferrocene was calculated as halfway between the oxidation and reduction peaks. This was calculated as $0.547 + 0.5 \cdot (0.625 - 0.547) = 0.586$ V.

Density functional theory calculations (DFT) were performed using Guassview 5.0 using an optimisation and frequency protocol in the ground state with B3LYP and the 6-31G basis set. Structures were subjected to preliminary optimisations both in Guassview and Chemdraw3D beforehand.

7.2 - Appendix II – Chapter specific supplementary materials

7.2.1 - Chapter 2

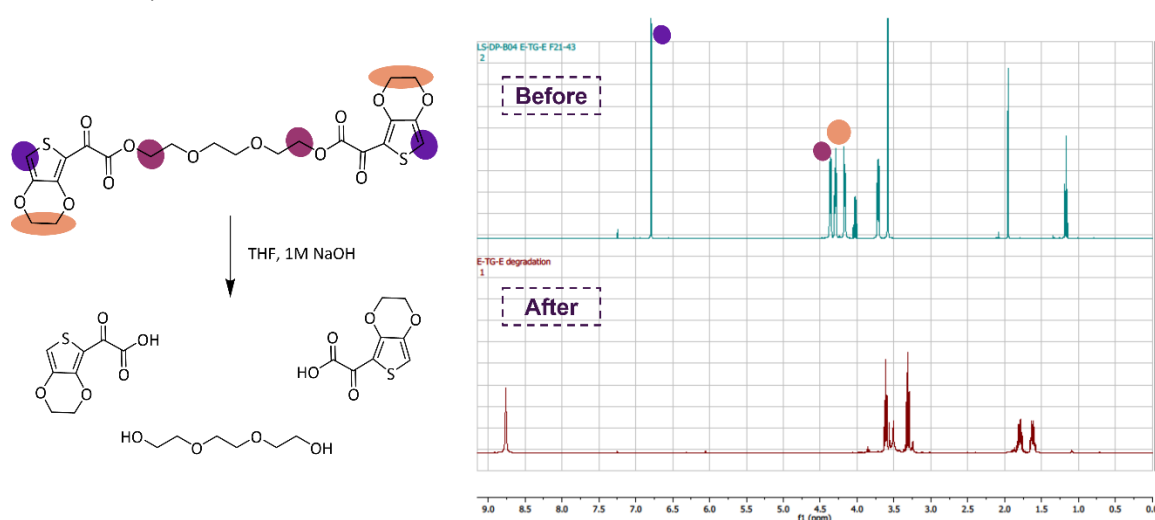


Figure A 1. ¹H NMR spectra showed the clear disappearance of peaks associated with EDOT and its coupling to triethylene glycol. Since EDOT portion is expected to form the EDOT-COOH illustrated it would likely not be soluble in CDCl₃ and as such is expected to absent from the resulting NMR.

7.2.2 - Chapter 4

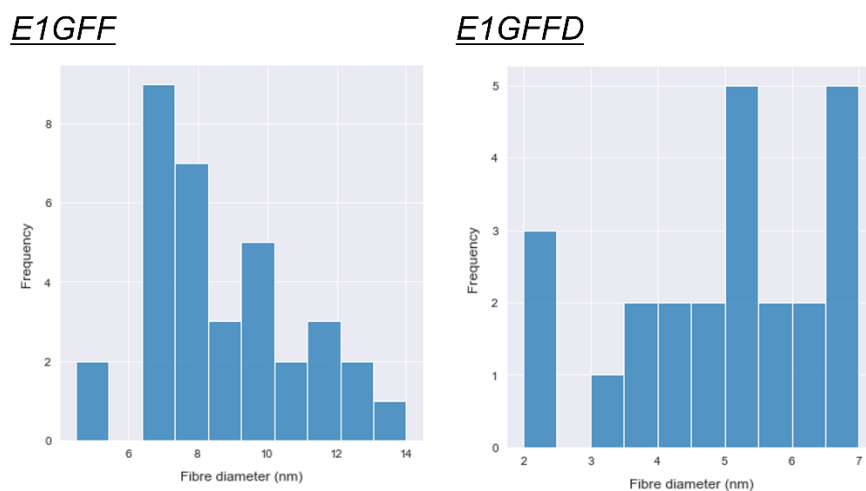


Figure A 2 – Histograms of the fibre diameters measured from diluted E1GFF and E1GFFD samples by AFM.

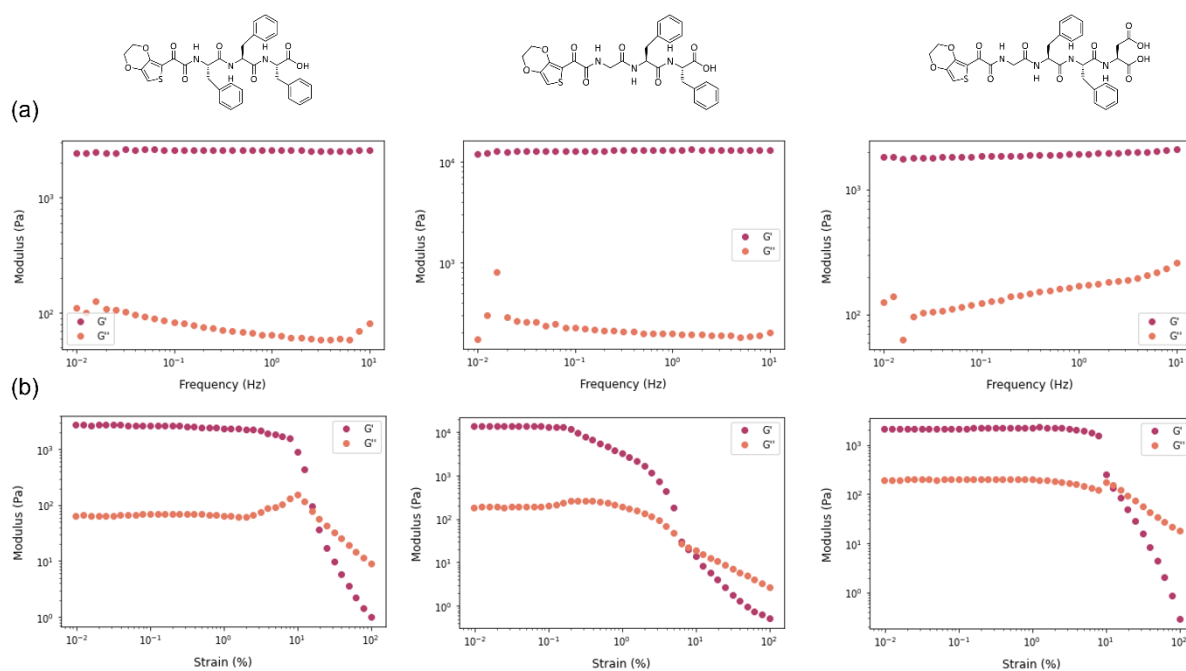


Figure A 3. Frequency (a) and strain (b) sweeps for each of the gelators. The data verifies that in each case the 1 Hz and 0.1 % strain used for the time sweeps were well within a region of consistency and so were probing an uncompromised sample.

7.2.3 - Chapter 5

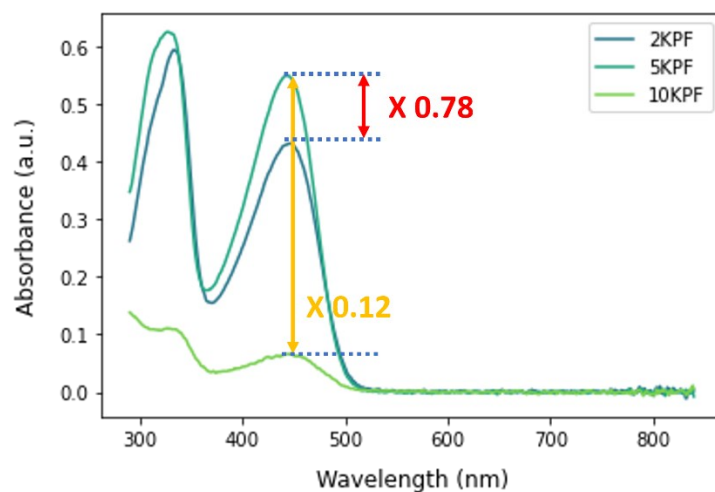
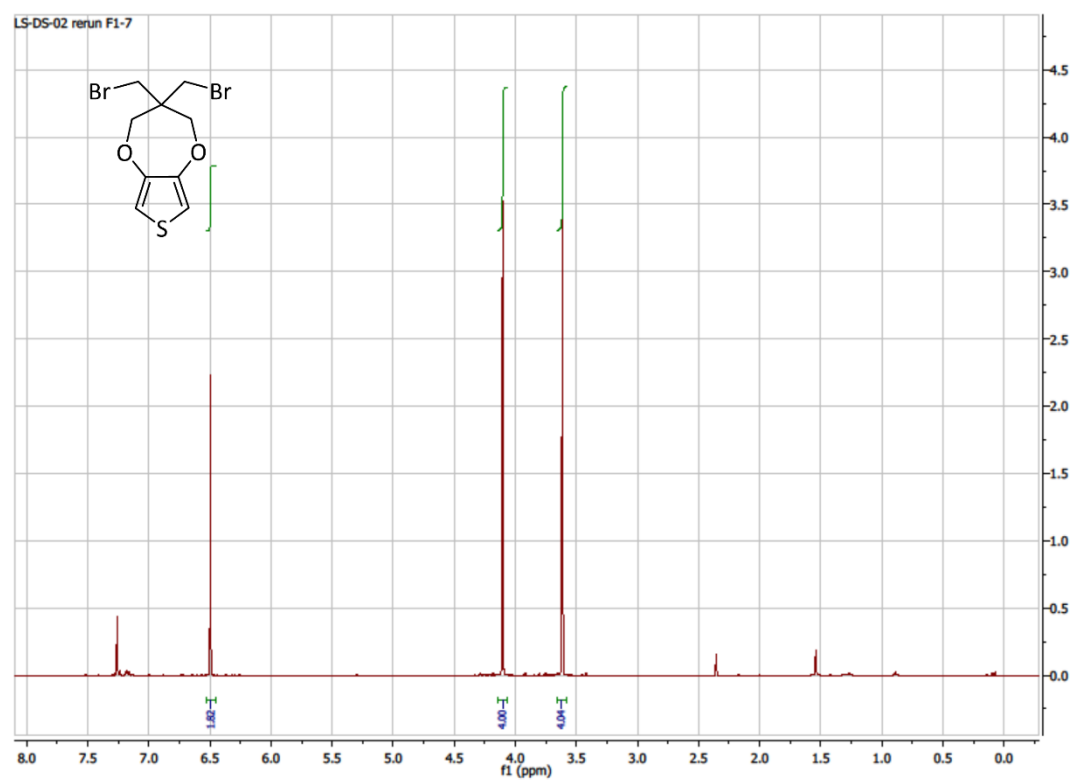


Figure A 4 - Estimation of the relative F8BT contents in each system. All samples were measured at 0.1mg/mL and were dissolved in THF in the 2K and 5K but in 1:1 THF:water in the 10K case owing to lack of solubility. Solubility was only estimated by eye as being properly dissolved in solution. Comparing peak values of 442 nm gives the ratios illustrated in the figure.

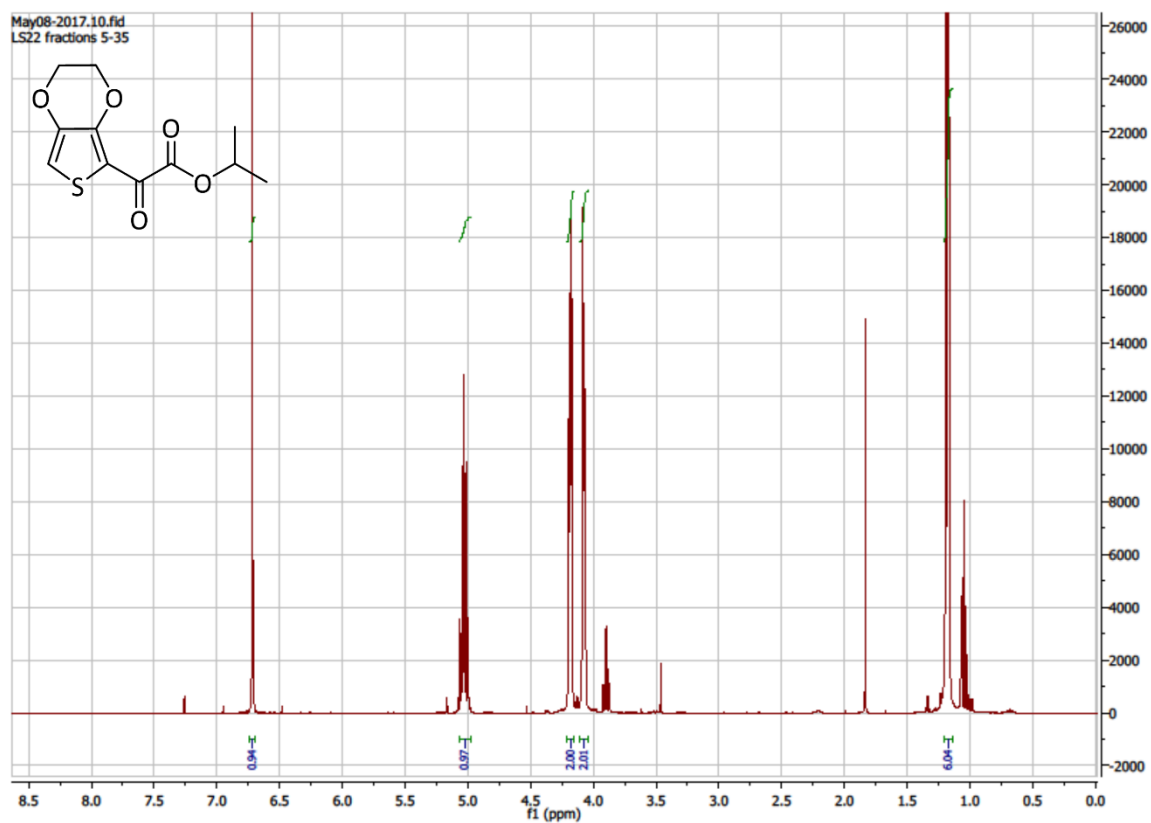
7.3 - Appendix III - NMR data

7.3.1 - Chapter 2 – NMR data

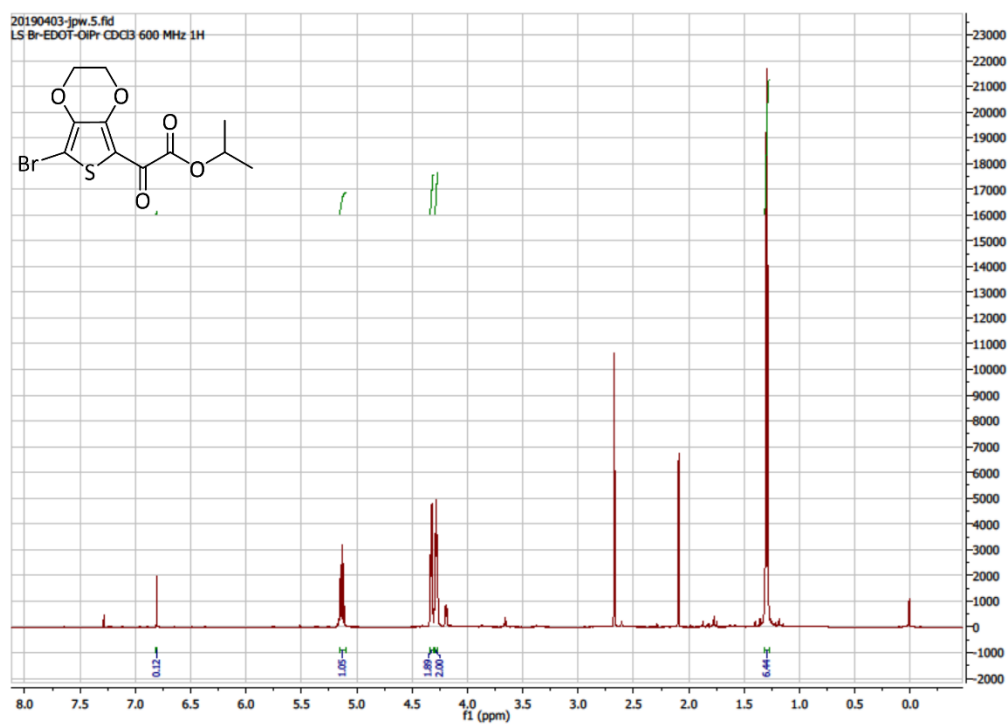
ProDOT(CH₂Br)₂ (**1**)



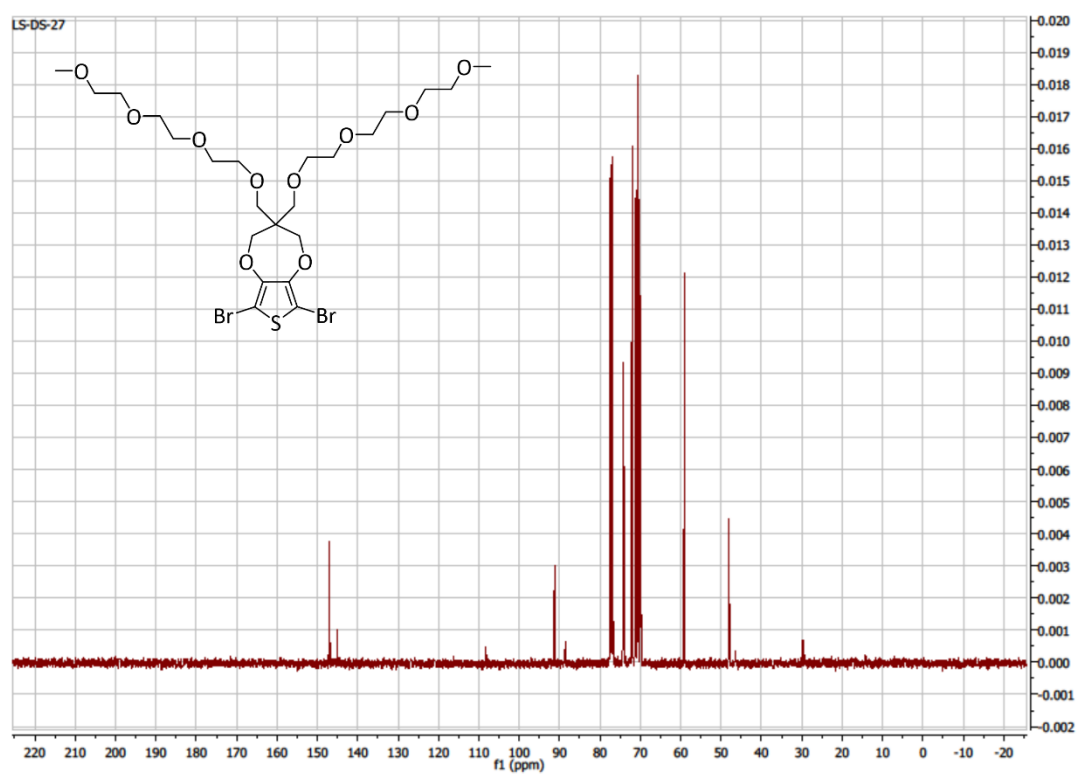
ProDOT(HD) (**2a**)



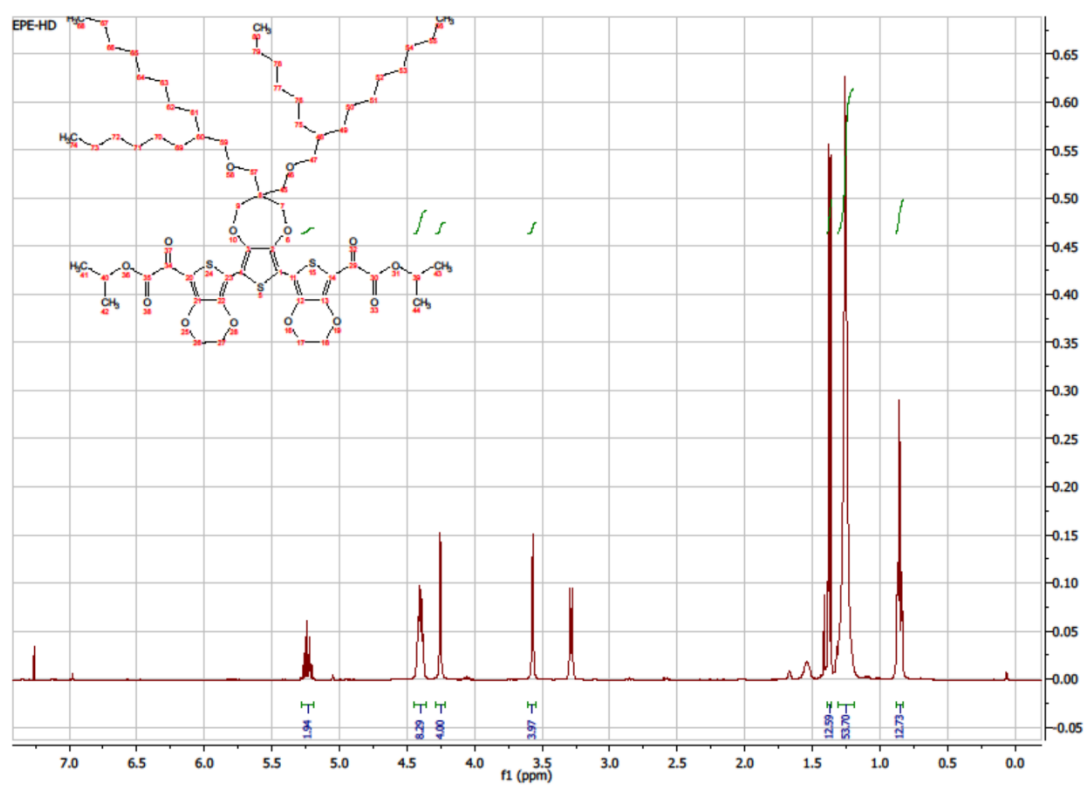
BrEDOT-OiPr: (4)

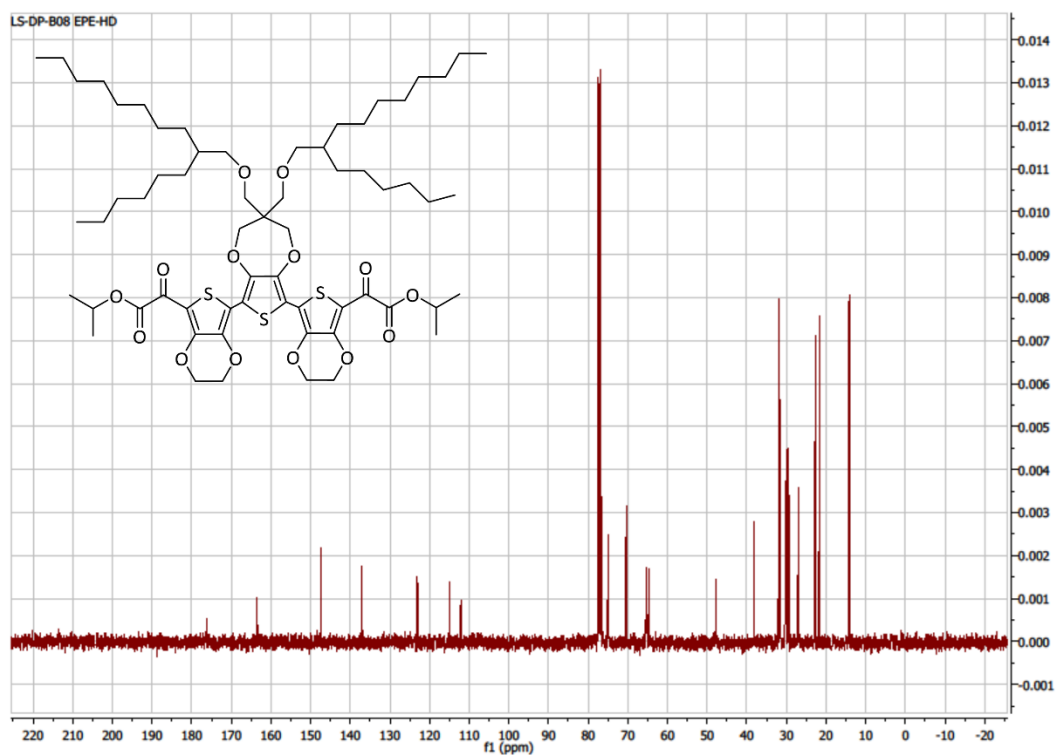


Br2ProDOT(HD) – not numbered, from alternative route – see chapter 2 experimental

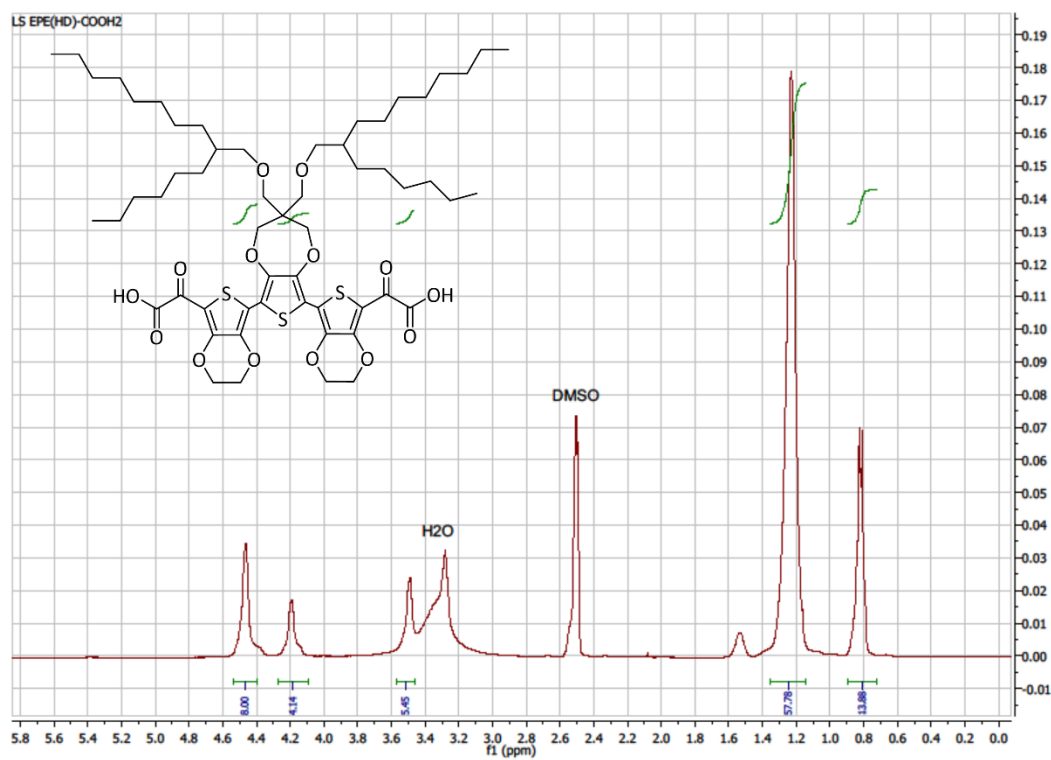


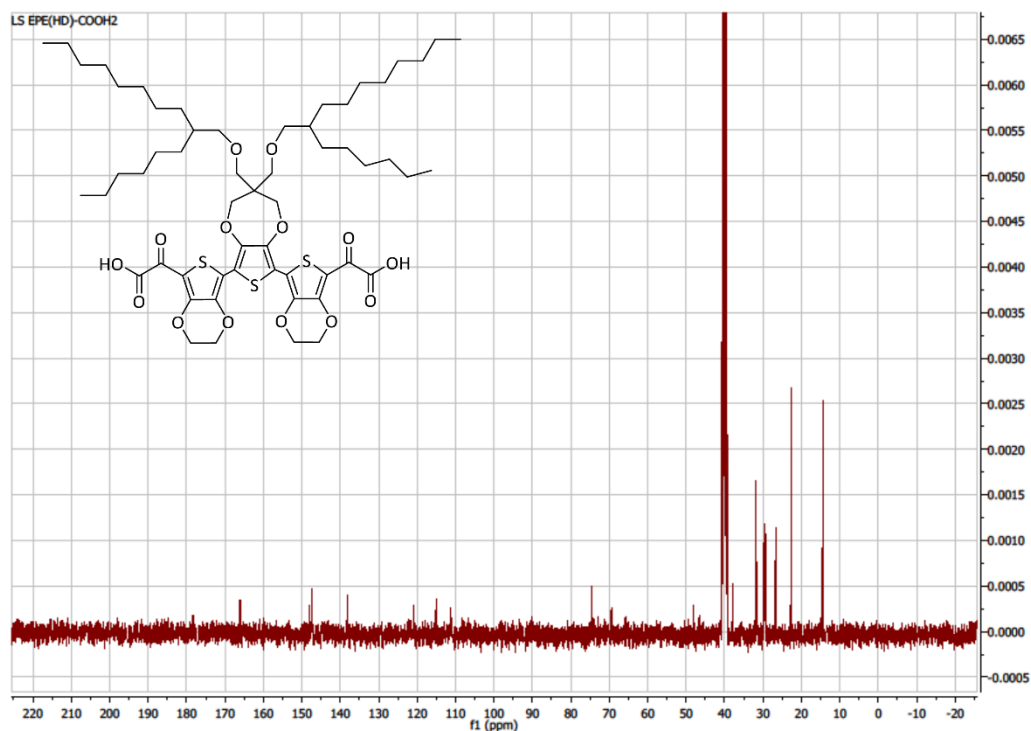
EPE(HD)-OiPr₂ (5a)



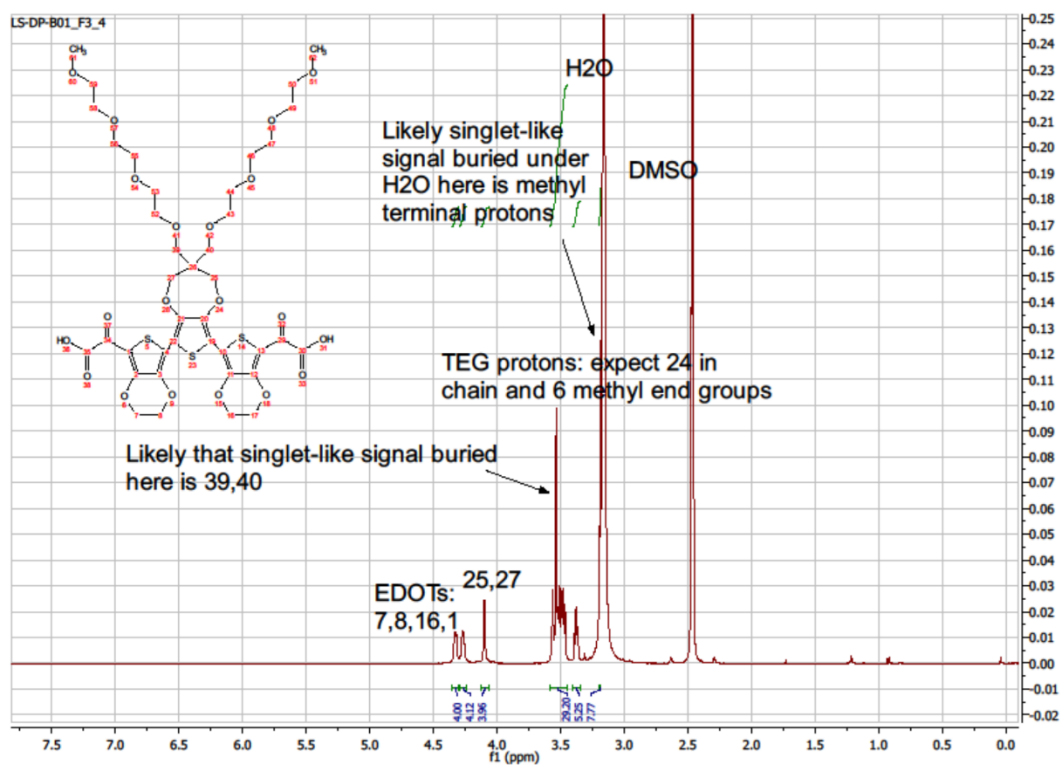


EPE(HD)-COOH2 (6a)

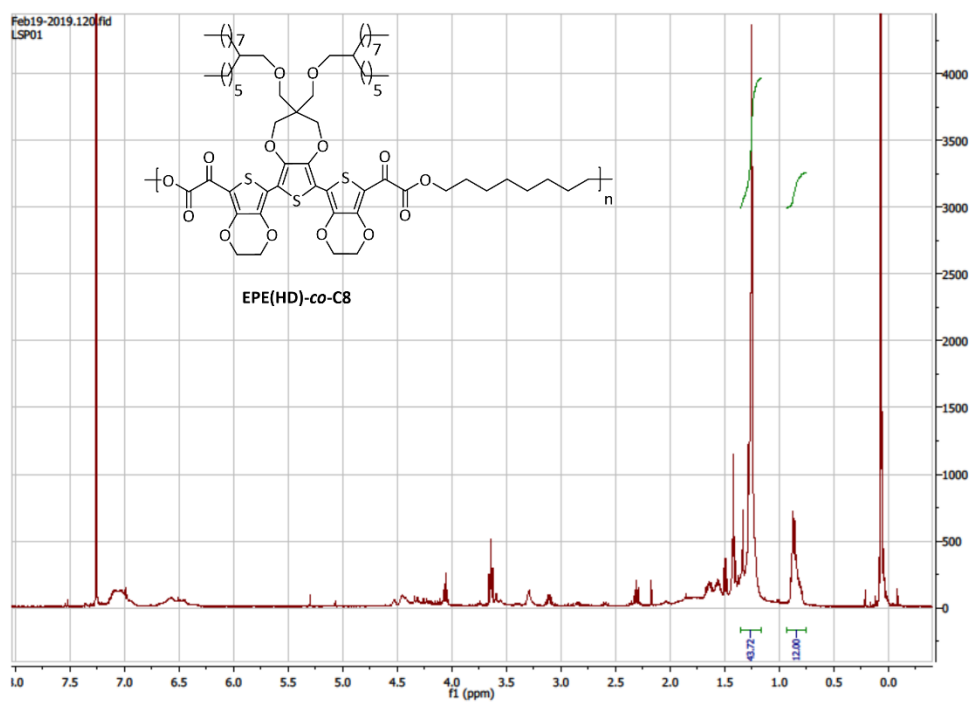




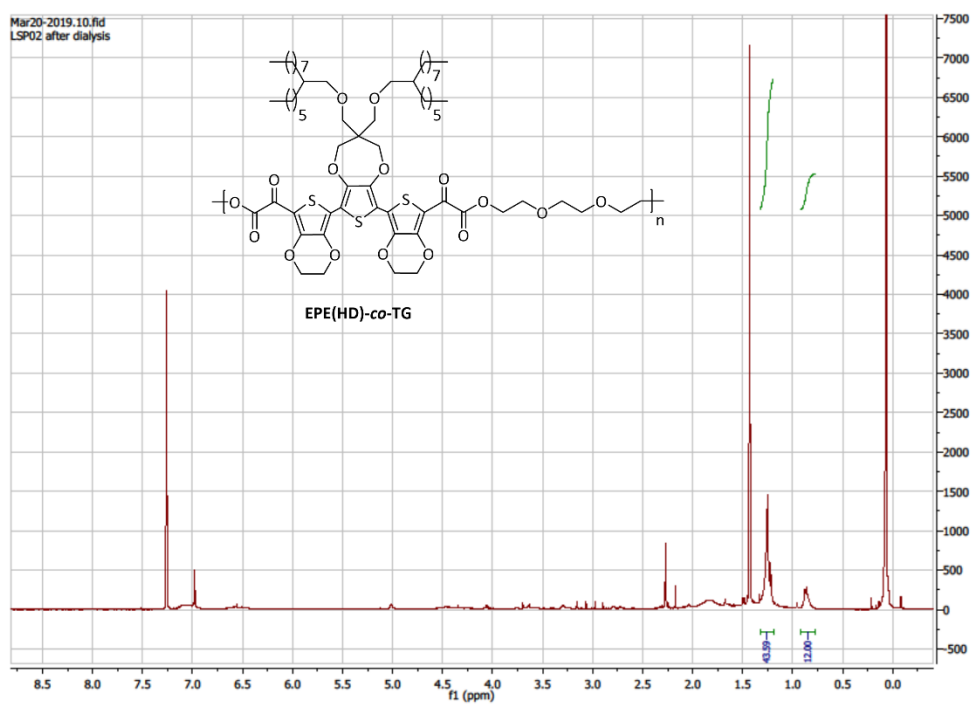
EPE(TG)-COOH2 (6b)



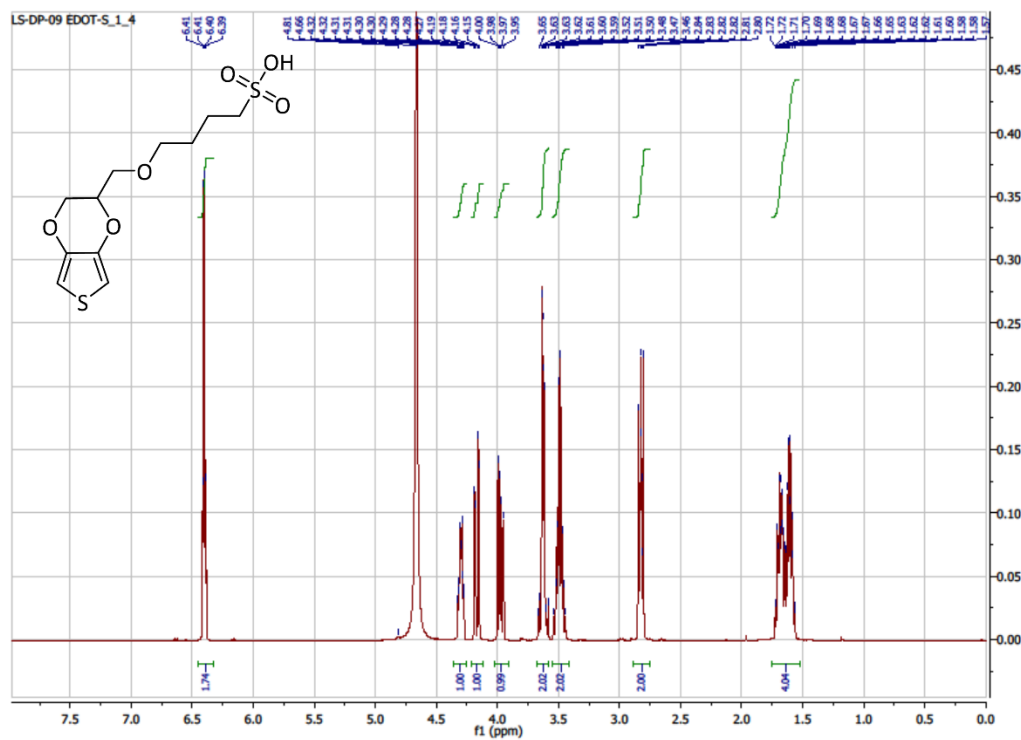
EPE(HD)-co-C8 (7a)



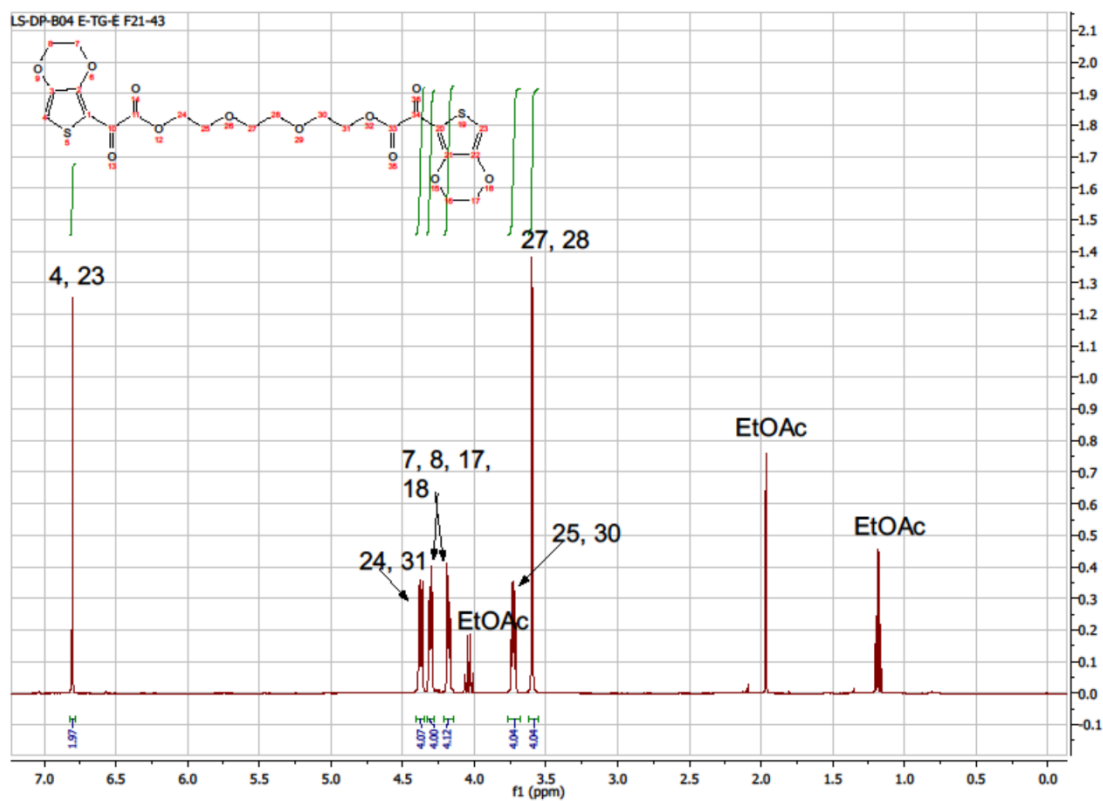
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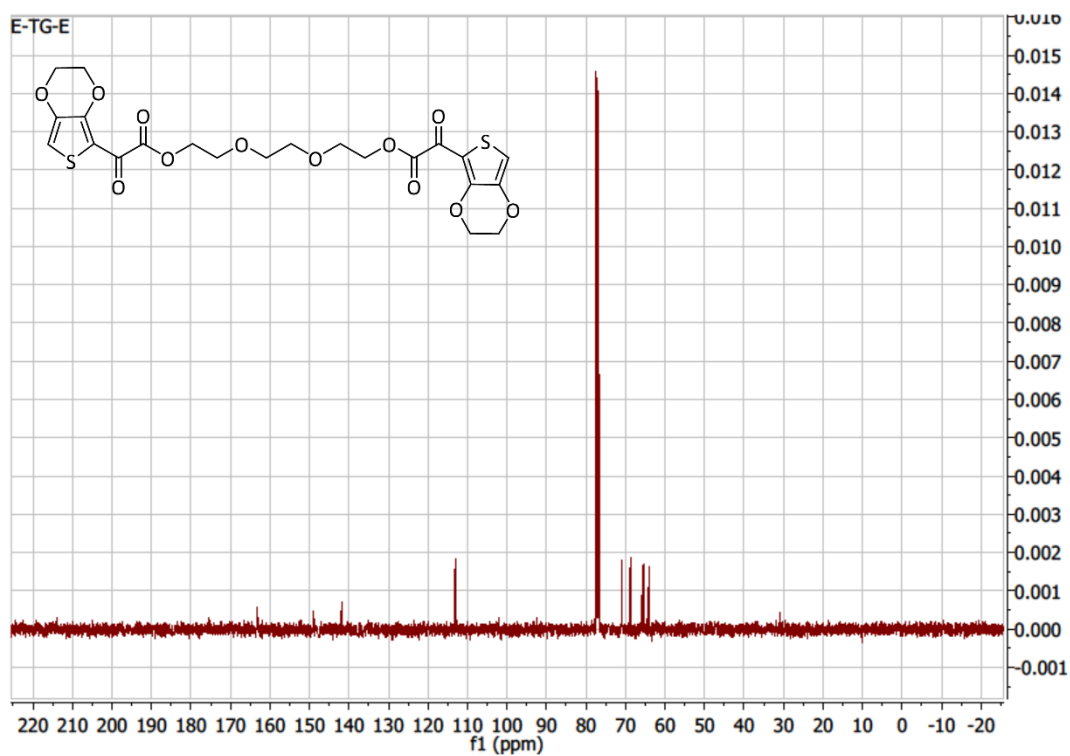


EDOT-S (8)



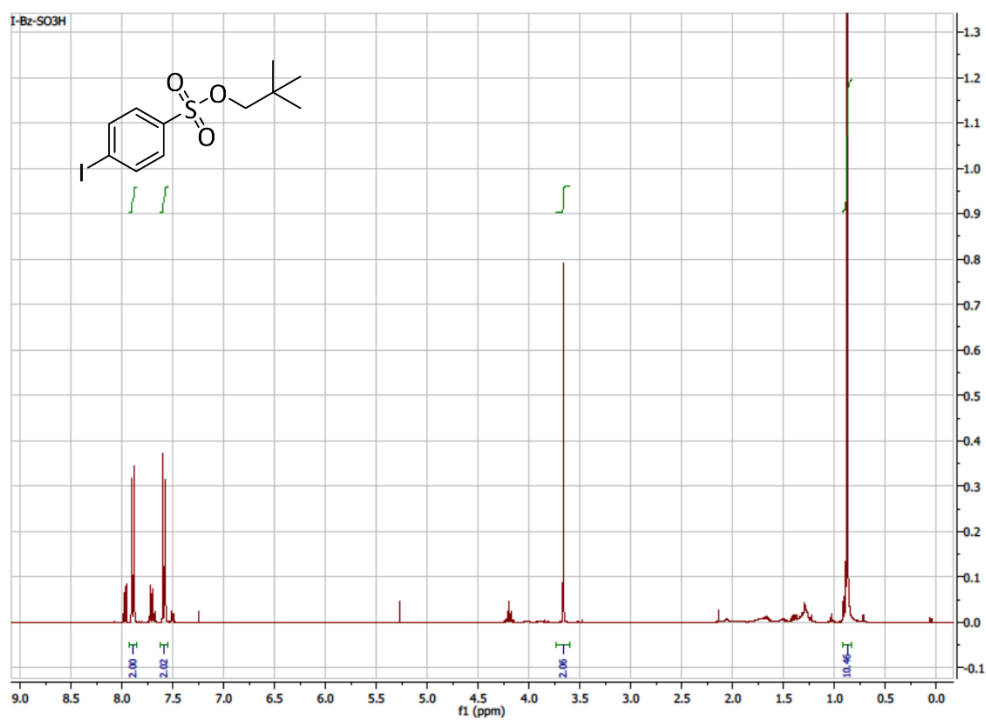
E-TG-E (9)

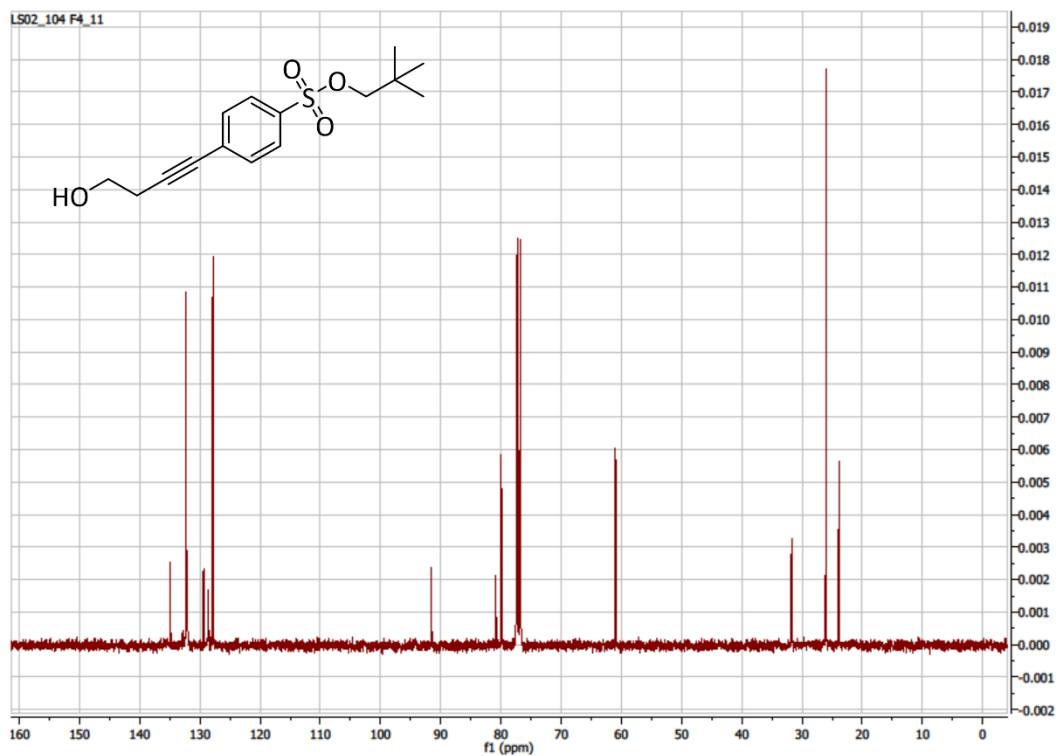




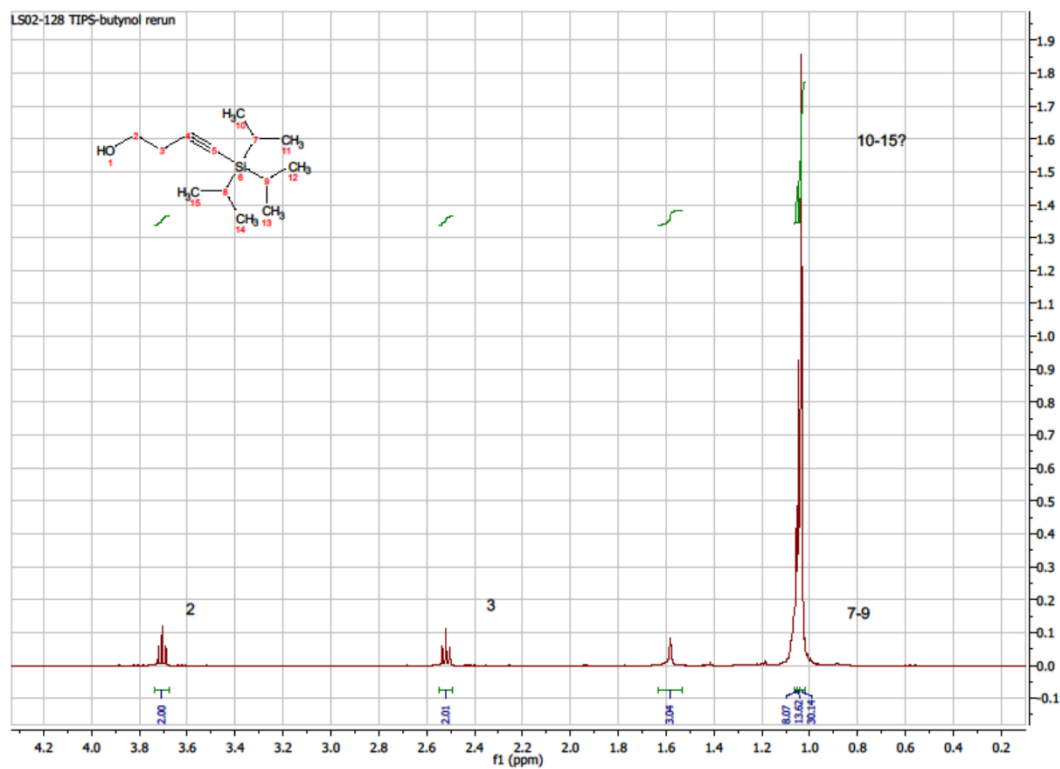
7.3.2 - Chapter 3 – NMR data

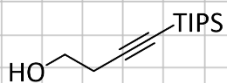
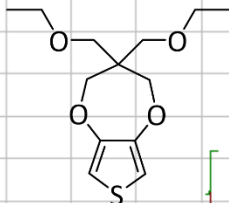
I-BS-Neo (**14**)

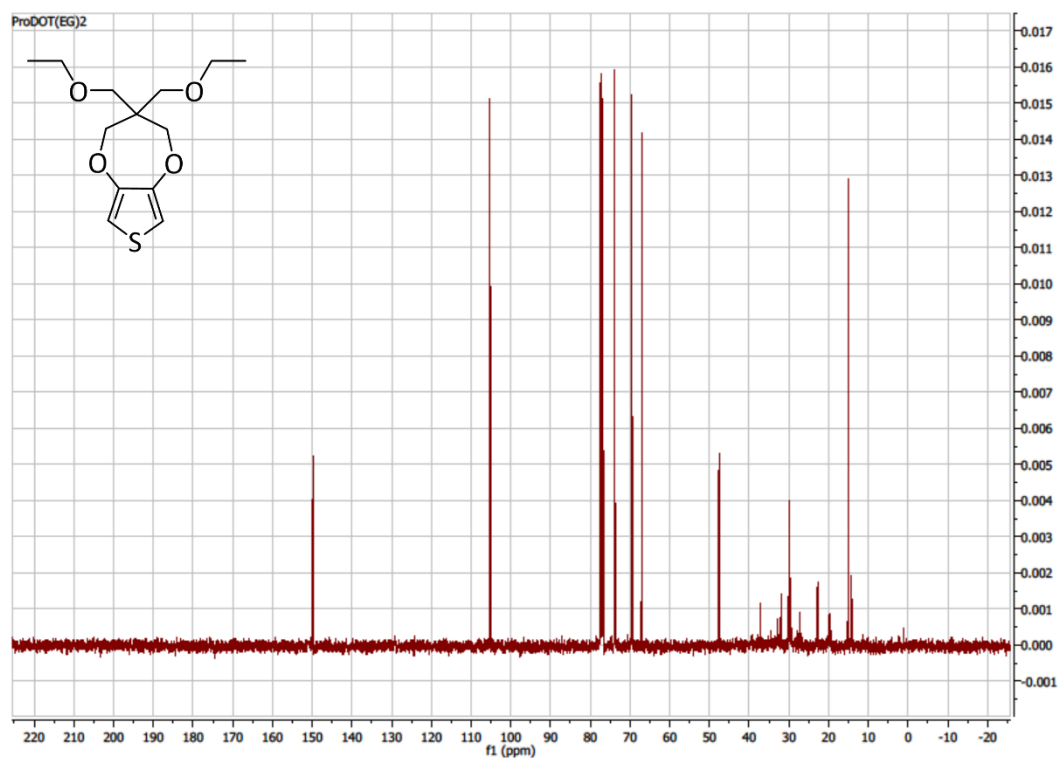




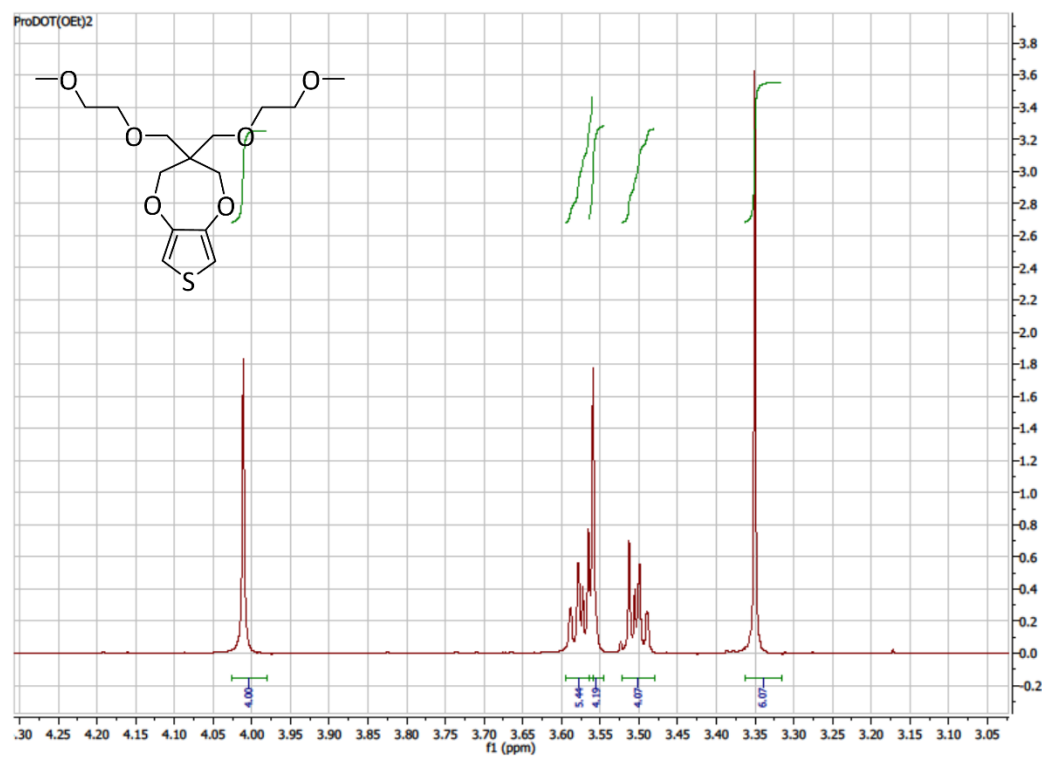
Butyne-TIPS (18)

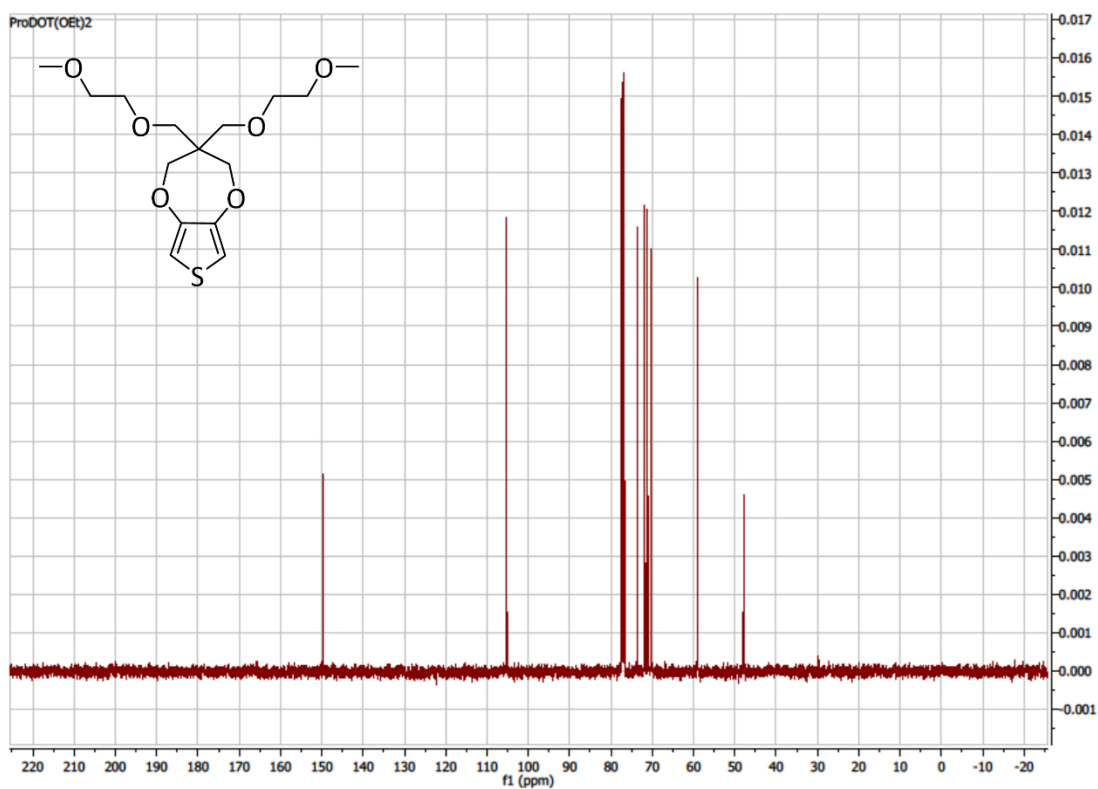


ProDOT(OEt)₂ (**21a**)

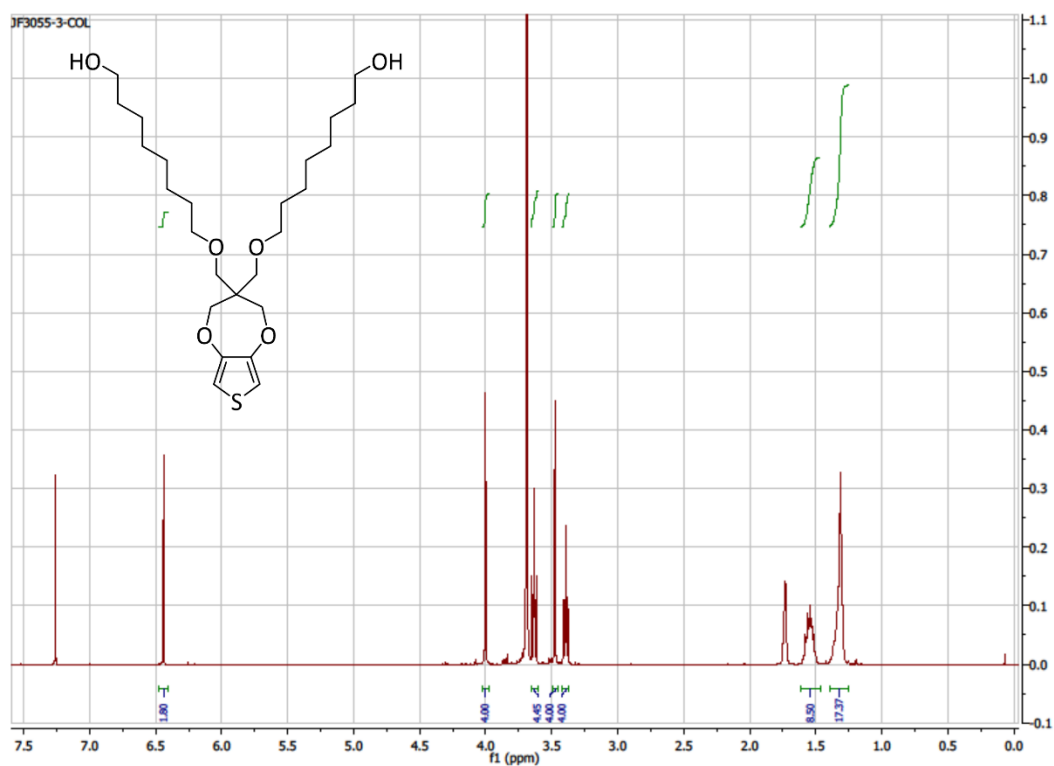


ProDOT(EG)2 (**21b**)

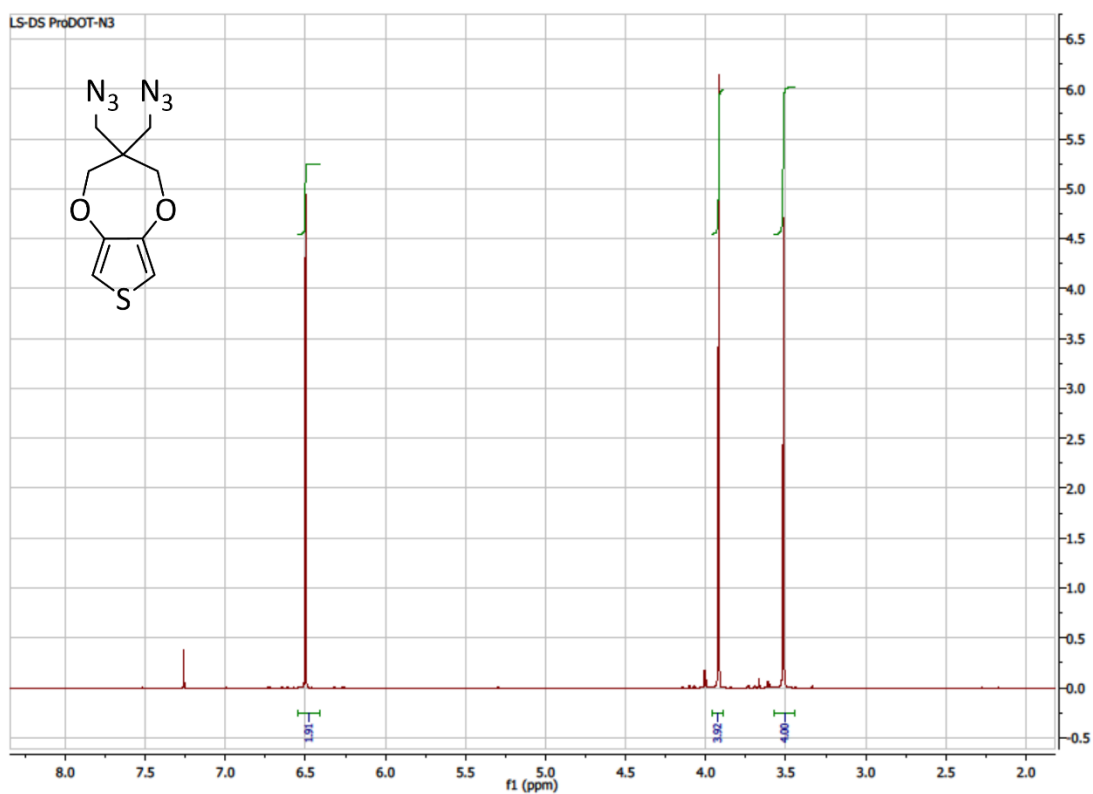




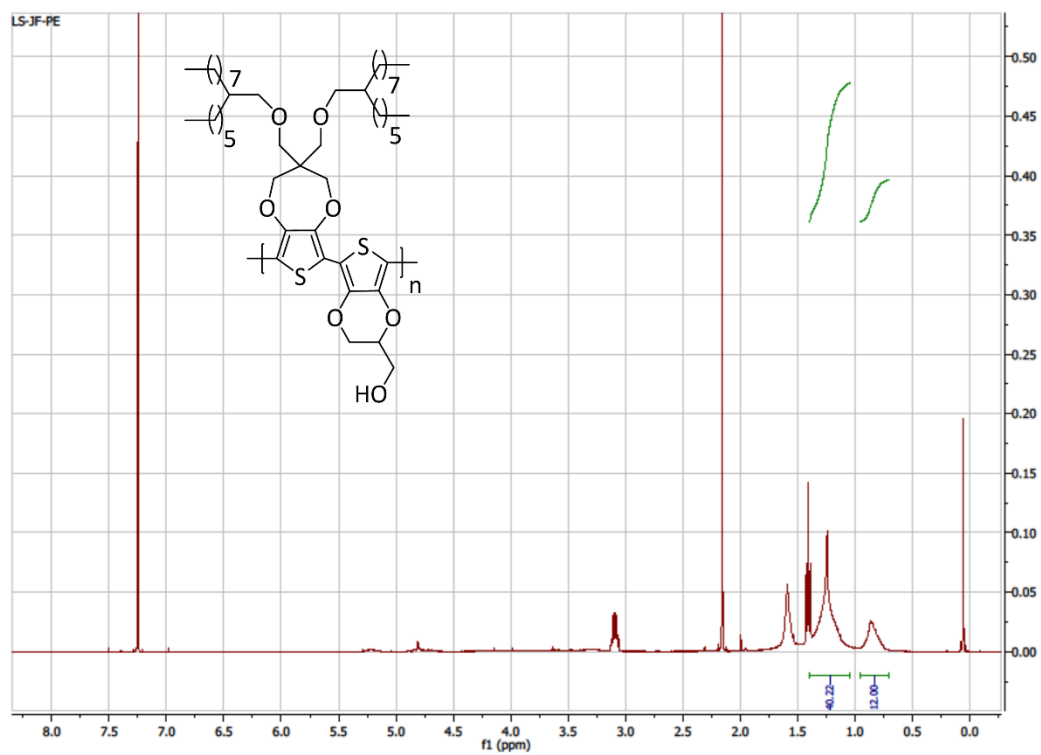
ProDOT(C8OH)₂ (**22**)



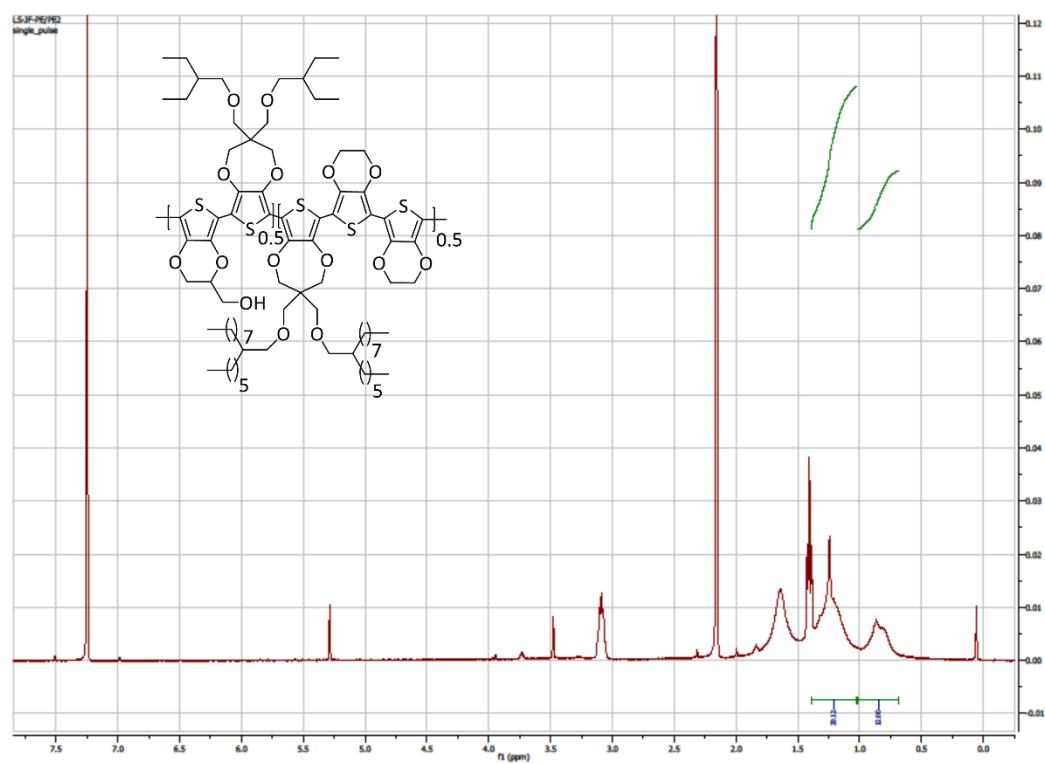
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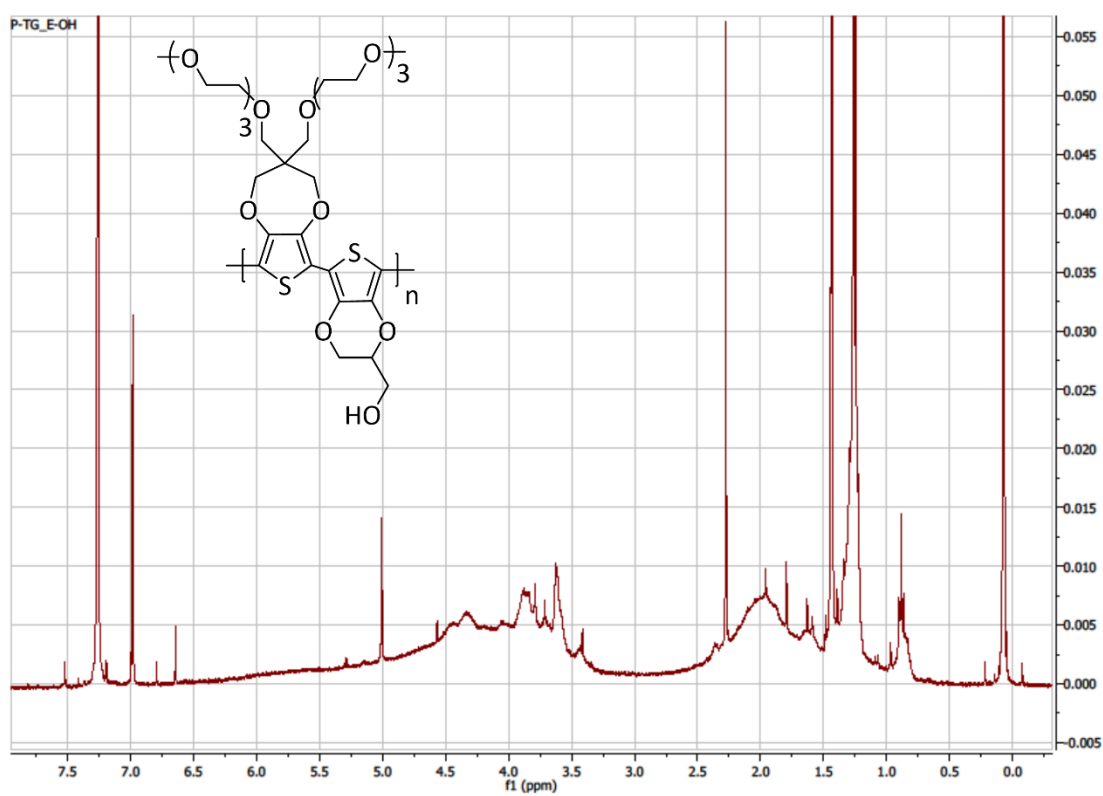
PE-OH

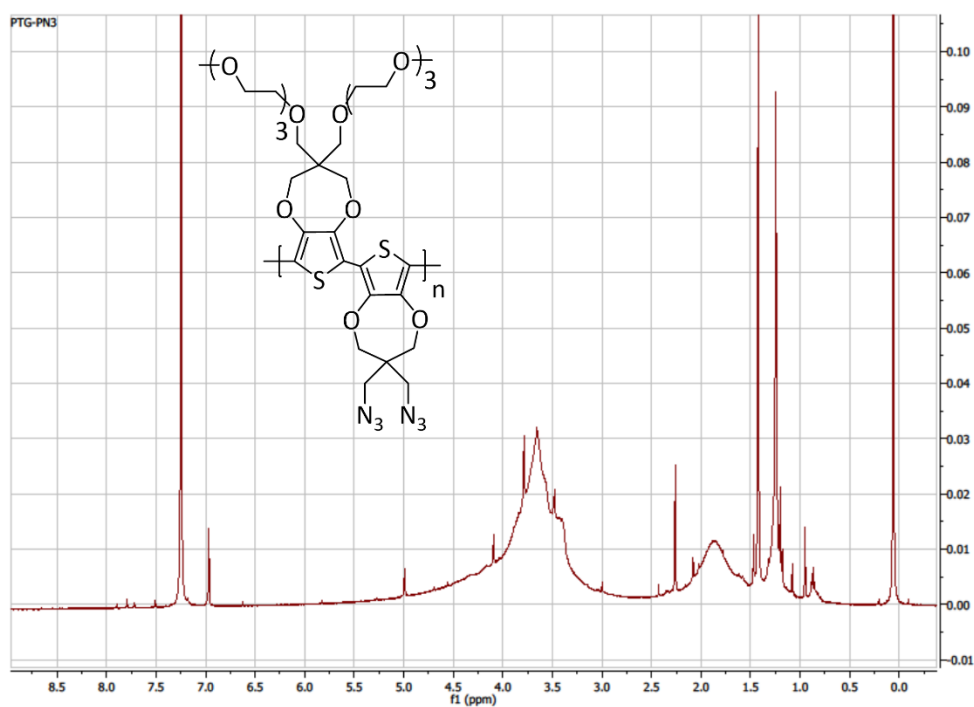


PE_PE2-OH



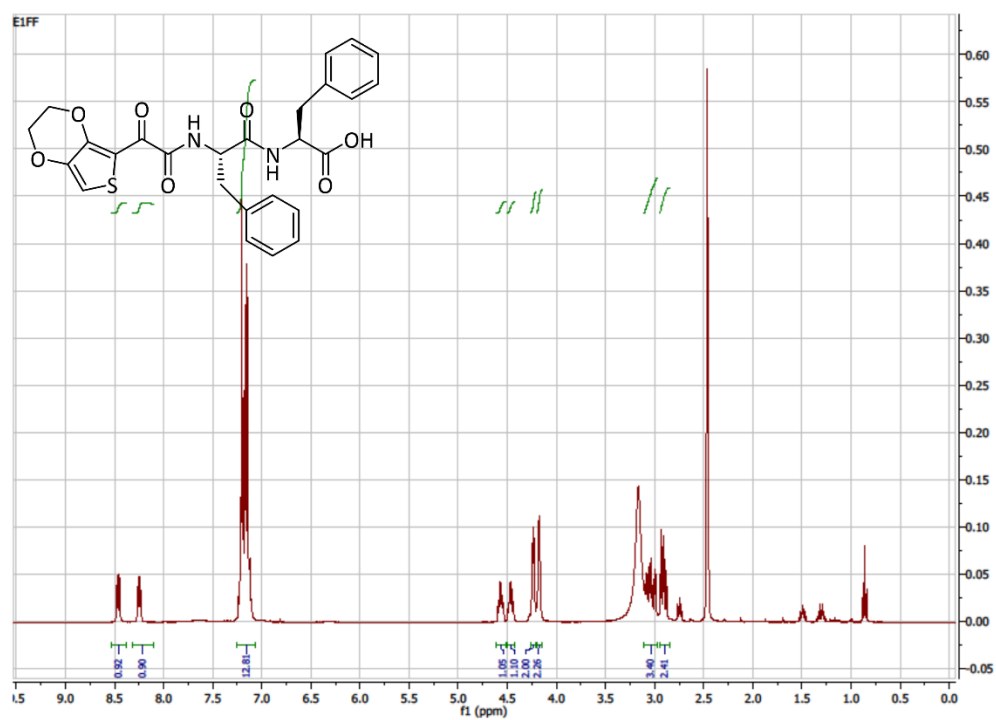
P(TG)-E(OH)

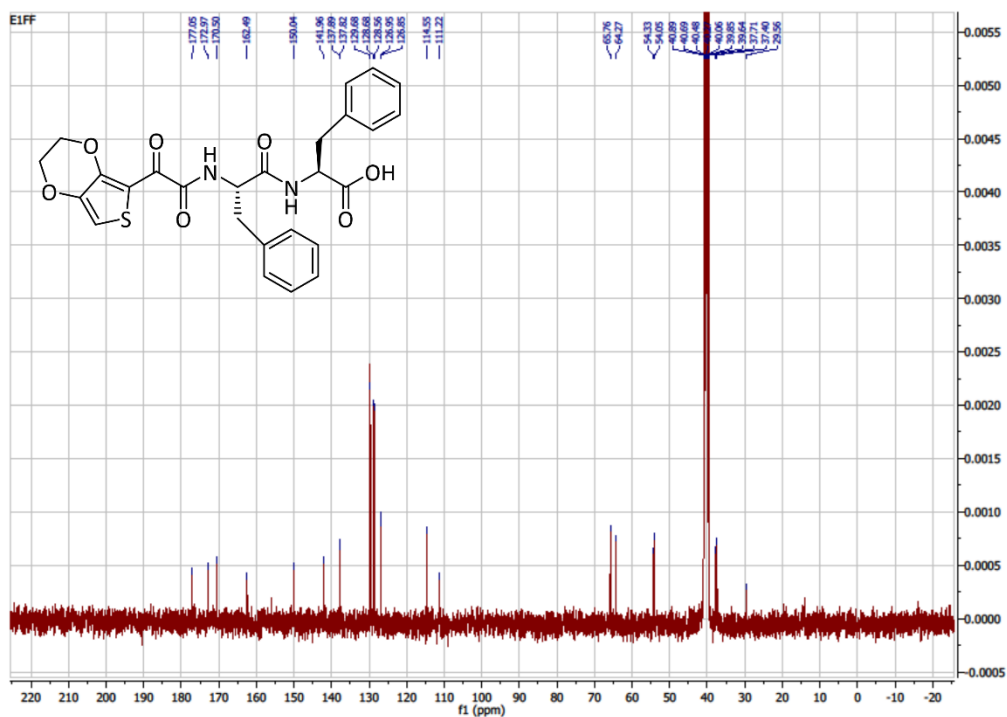




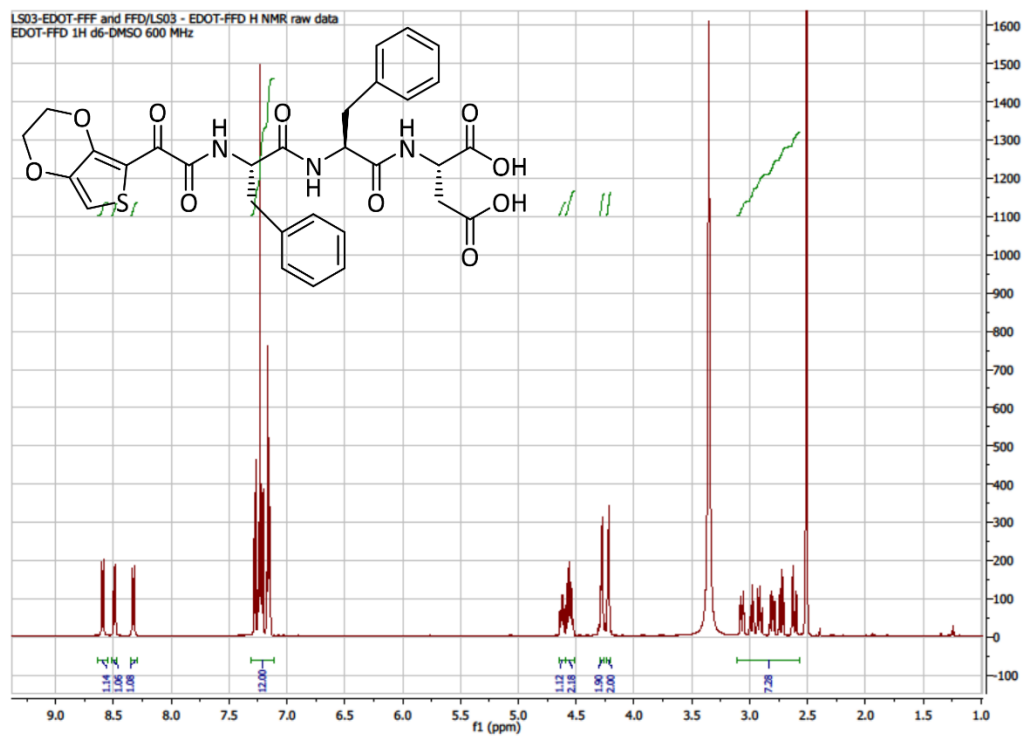
7.3.3 - Chapter 4 – NMR data

E1FF

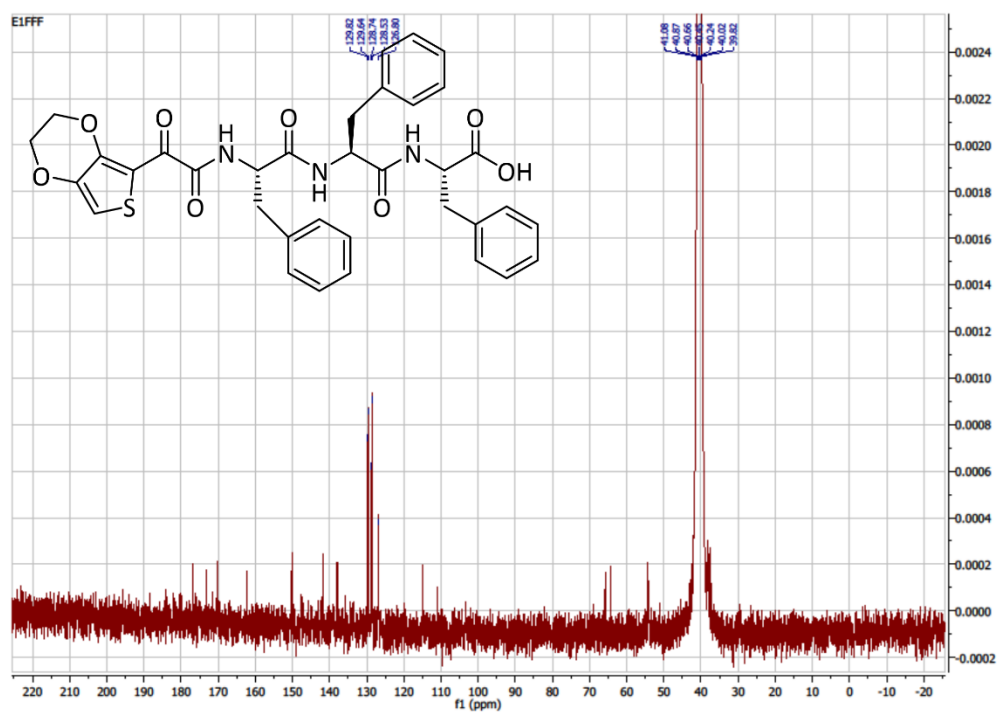
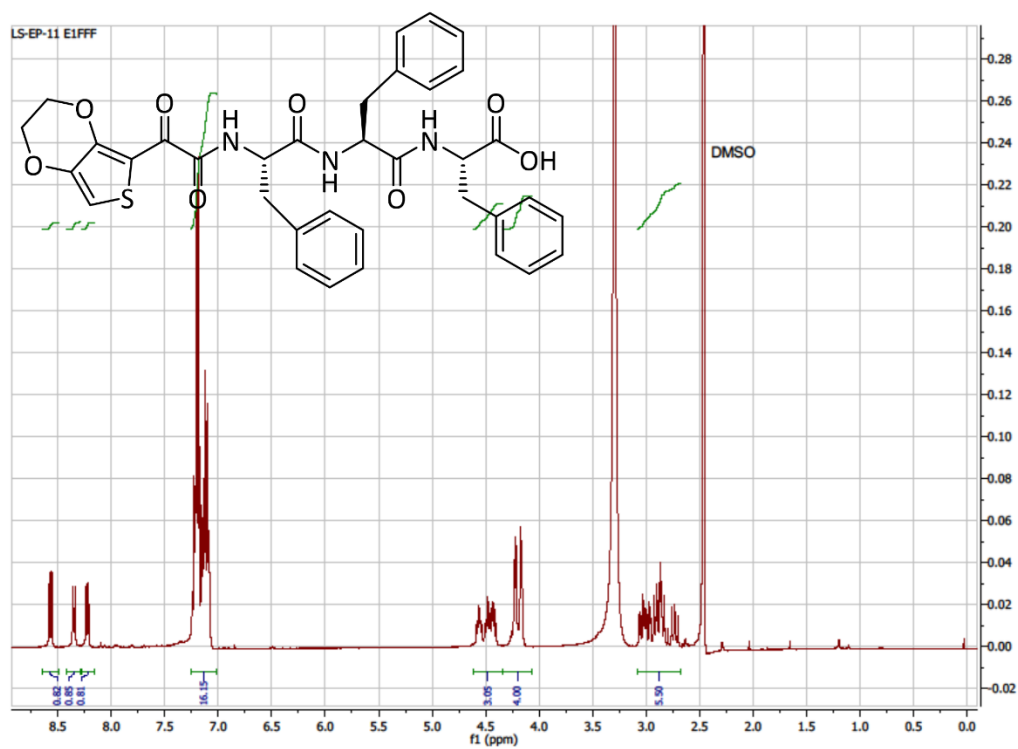




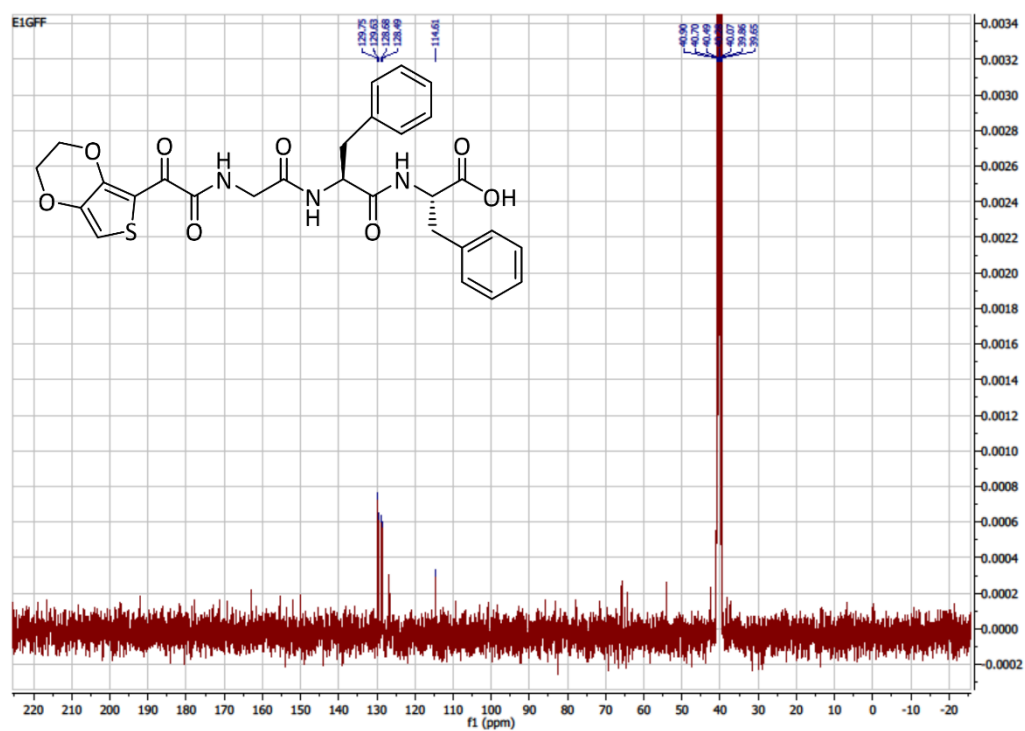
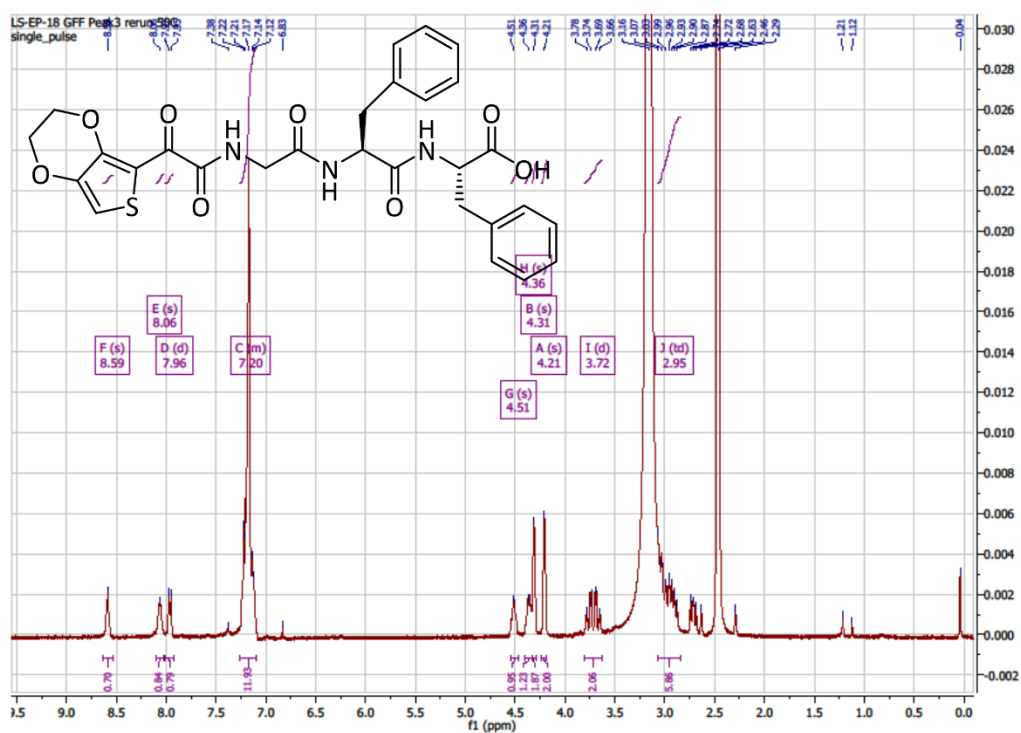
E1FFD



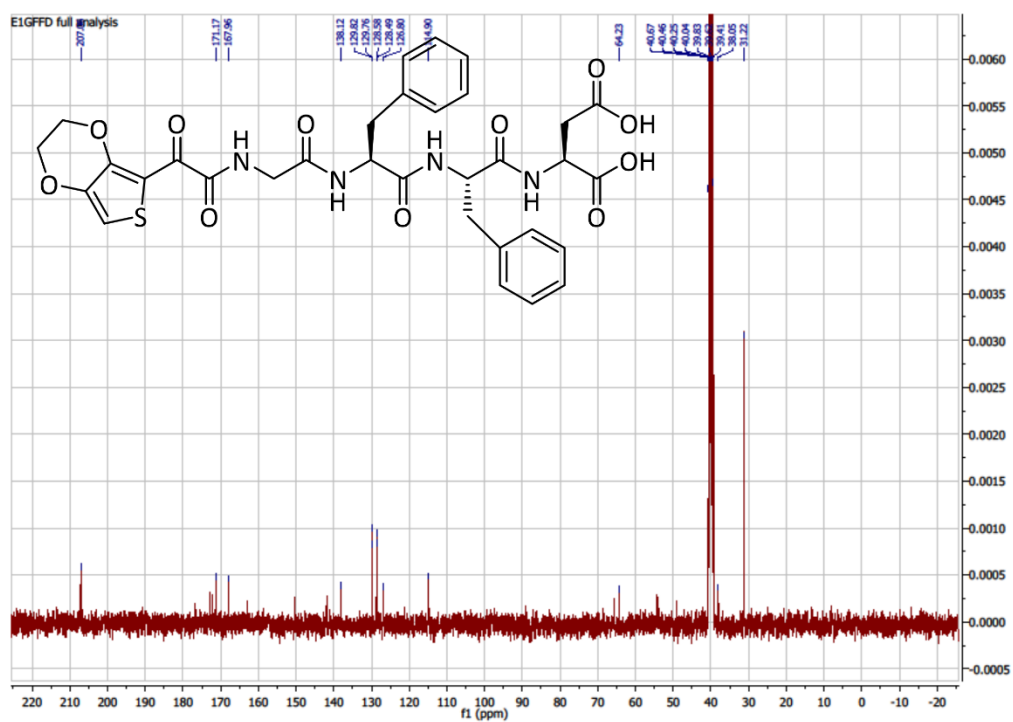
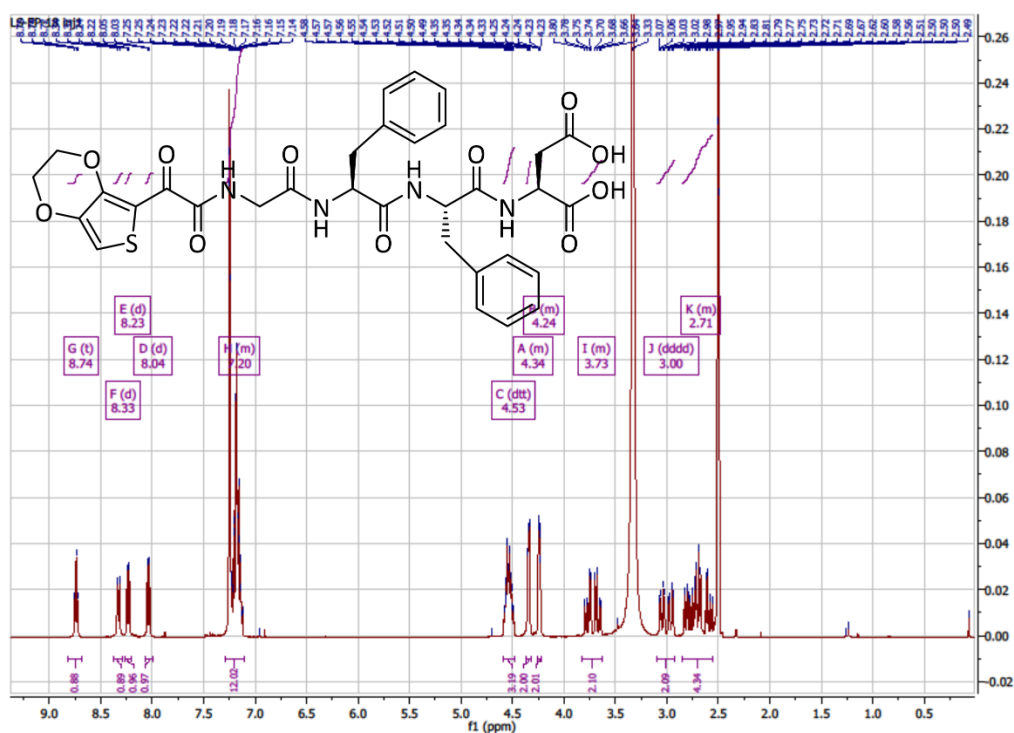
E1FFF



E1GFF



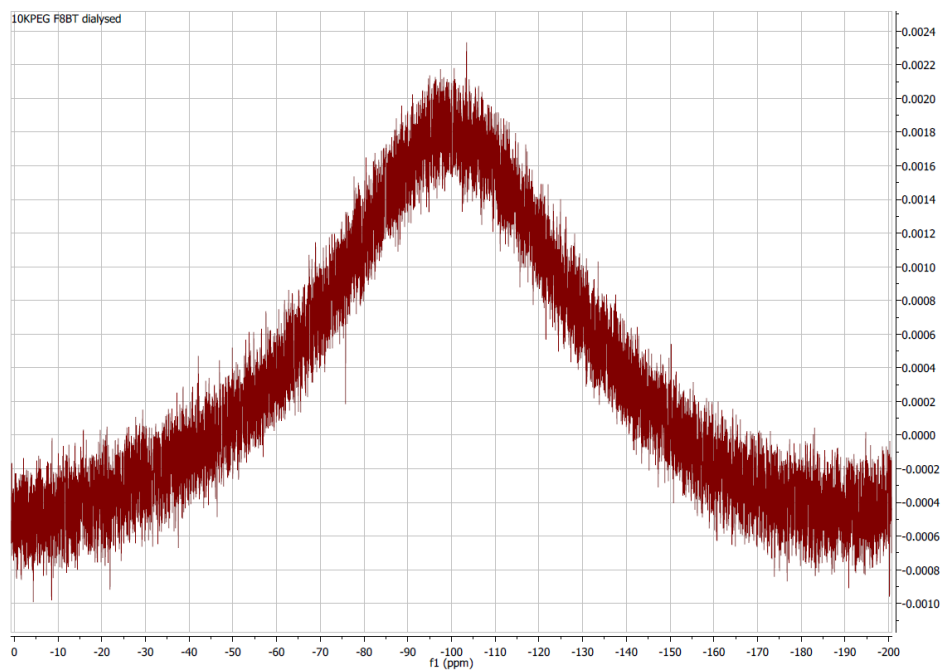
E1GFFD



7.3.4 - Chapter 4 – NMR data

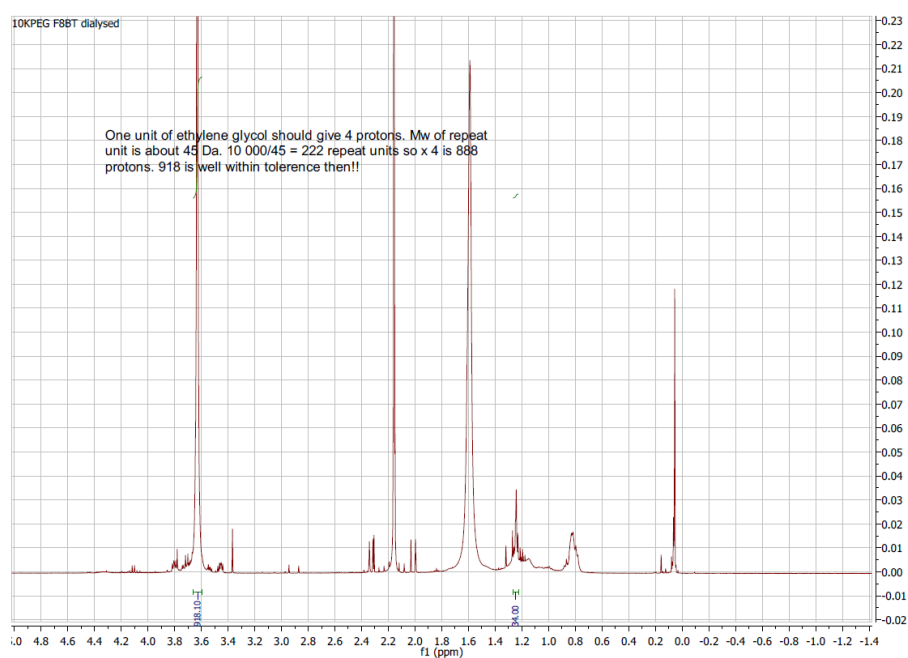
Poly(9,9-dioctylfluorene-*alt*-benzothiadiazole)-*g*-Poly(ethylene glycol)-10 000

¹⁹F-NMR



Note the absence of significant signal implying fluorines on the backbone have been successfully displaced through S_NAr .

¹H-NMR



The correct ratio of PEG to F8BT protons is seen within tolerable error.

7.4 - Permissions

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Chapter 1 – Figure 1-6

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